AMERICAN JOURNAL OF PHARMTECH RESEARCH
Journal home page: http://www.ajptr.com/

Fast Disintegrating Tablet Containing Cassia Angustifolia (Senna)

V Sai Shivram[1], Dalavi Vishal[1]*, Mandavkar Yuvaraj[1], Deshmukh Swapnil[1]
1. Research & Development, Tulip Lab. Pvt.,Ltd.-Ranjangaon, Pune, India.

ABSTRACT

Cassia angustifolia is popularly known as senna, since its leaves and pods are common laxatives, they are widely used in medicine and as a household remedy for constipation all over the world popularly in Europe and US. It is available in various dosage forms such as tablets, capsules, granules, liquids and in combination with other laxatives. The objective of the present research work is to develop a preservative free formulation with direct compression approach, complying to USP dissolution test, microbiological purity and standards of heavy metals laid down by WHO. The tablets prepared by direct compression approach are economical, have minimum processing steps, faster disintegration, rapid onset of action and complying to all other tablets parameters.

Keywords: Heavy metal, microbial count, preservative free, senna extract, USP dissolution.

*Corresponding Author Email: fnd@tlplindia.com
Received 05 February 2015, Accepted 11 March 2015

Please cite this article as: Dalavi V *et al.*,Fast Disintegrating Tablet Containing Cassia Angustifolia (Senna). American Journal of PharmTech Research 2015.

INTRODUCTION

Cassia angustifolia Vahl popularly known as Senna belong to family Caesalpiniacea having botanical classification as Planate Division: Magnoliophyta, Class: Magnoliopsida, Genes: Cassia, Species: *C. Angustifolia*[1]. *C. acutifolia* is native to Egypt and the Sudan while *C. angustifolia* is native to Somalia, the Middle East and India. Plants known as wild senna (*C. hebecarpa* Fern. and *C. marilandica* L.) grow on moist banks and in woods in the Eastern United States[2]. Senna is excellent laxative besides this it is used as expectorant, wound dresser, carminative agent. It is also used in the treatment of malaria, jaundice, anaemia and skin diseases all over the world. It is one of the important plant drug in ayurvedic and modern system of medicine and which is appproved by the U.S. Food and Drug Administration, as a non-prescription laxative and cathartic for the treatment of constipation and for bowel evacuation[3,4]. Senna is also mentioned in World Health Organization's list of essential medicines. Senna does have one potential safety advantage over other herbal anthranoid laxatives, its particular anthranoids are not very absorbable, this reduces the potential harmful risk to the body[5]. Constipation is a common complaint in about 6% of the middle-aged population and 20-80% of the elderly people, and may be treated by laxatives. Constipation also tends to be more prevalent among women[6]. It is a main symptom of irritable bowel syndrome in all ages, the functional constipation is the most common type without any specific etiology. Senna formulations are available in various dosage forms like tablets, capsules, granules & liquid with the addition of preservatives. The granules & liquid dosage forms have some draw backs like they are not available in unit dose formulation and difficult to administer. The biggest challenge in developing oral laxative formulation is to have rapid onset of action which is required for faster pharmacological effect. Marketed formulations of senna does not have faster disintegration time. The activity of laxative formulation is enhanced when it comes in contact with fluid/water. Another challenge in developing a herbal formulations is to have microbiological purity till the end of shelf life. Parabens, benzoates, butylated hydroxyanisole etc are the commonly used preservatives in the marketed products added to control the microbial bioburden of the formulation, which are known to causes allergies, liver diseases and may damage brain and they are carcinogenic in nature[7]. In spite of the advantages afforded by wet granulation, many manufacturers would welcome the opportunity to directly compress the tablets. There is a need in the industry for using techniques and appropriate pharmaceutical excipients which allow manufacturers to prepare a tablets by direct compression which minimize processing time/reduces steps, labour and energy costs for manufacture and the avoid water for granulation of water

sensitive drug substances[8]. Majority of people believe that herbal medicines are safe and nontoxic, unlike modern chemotherapeutic agents. On contrarily, it has been reported that one out of five Ayurvedic herbal medicine products (HMPs) used and produced in the South Asia (Indian subcontinent and China) contain higher concentration of heavy metals (lead, mercury, and arsenic) than in other areas and also they contain higher amount of microbial load than the acceptable limit[9-12]. Hence in the current research work, preservative free formulation of senna extract was developed by direct compression approach which has faster disintegration, complying to parameters as per USP such as dissolution, microbiological purity and also complying to the standards of heavy metals laid down by WHO.

MATERIALS AND METHOD

Senna extract containing 20% calcium sennosides was procured from Phytoconcentrate, Gujarat. Excipients like Microcrystalline Cellulose, Dibasic Calcium Phosphate, Mannitol, Sodium Starch Glycolate, Colloidal Anhydrous Silica and Magnesium Stearate have monographs in European and British pharmacopoeia. None of the excipients used contain material of animal or human origin.

Formulation Development of Senna Tablets

The dry powder blend was evaluated for various physical properties like tapped density, bulk density, Hausner ratio and compressibility index[13,14]. Tablets were compressed using a single rotary tablet compression machine (Fluid Pack, 10 stations), with 10 mm punch tools. The composition of the tablets is mentioned in Table 1.

Table 1: Composition of various tablet formulations containing senna extract

	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)
Senna extract (20 mg calcium sennosides)	42.8	42.8	42.8	42.8	42.8	42.8
Microcrystalline cellulose	126.2	136.7	134.2	129.2	126.7	126.2
Calcium hydrogen phosphate	45.0	63.0	-	-	-	-
Mannitol	31.0	-	63.0	63.0	63.0	63.0
Sodium starch glycolate	-	2.5	5.0	10.0	12.5	13.0
Colloidal anhydrous silica	2.5	2.5	2.5	2.5	2.5	2.5
Magnesium stearate	2.5	2.5	2.5	2.5	2.5	2.5
Total (mg)	250.0	250.0	250.0	250.0	250.0	250.0

Physical Parameters

The compressed tablets were evaluated for physical parameters like thickness, weight variation, hardness, friability and disintegration time[14-16].

Heavy Metal Analysis

Heavy metal analysis of formulation was performed by Atomic absorption spectroscopy (AAS) as per WHO and Ayush guideline.

Microbial Test

The microbial count of the formulated tablets was performed as outlined in British and US Pharmacopoeia for the presence of bacteria as well as for fungi. Total count of bacteria and fungi was calculated using plate count method.

In Vitro Drug Release

The release of drug from formulated fast disintegration tablets was determined using USP type I dissolution apparatus at 100 rpm in 900 ml of water maintained at 37 ± 0.5°C for 120 min. A sample (5 mL) of the solution was withdrawn from the dissolution apparatus at specific time intervals, and the samples were replaced with fresh dissolution medium. The drug content of sample was analyzed using fluorescence spectrophotometry.

Accelerated Stability Study

Generally, a finished product should be evaluated under storage conditions that test its thermal stability and if necessary its sensitivity to moisture and potential for solvent loss. The optimized formulation (F6) of the drug was packed in HDPE container and stability studies were carried out as per ICH guidelines at accelerated storage condition (40±2ºC/75±5 %). The microbiological attributes were determined at the end of accelerated stability study. and relative humidity at RH 75+5 % in order to determine the change in microbial count[17].

RESULTS AND DISCUSSION

The key to direct compression is selection of an appropriate excipients. Direct compression formulations can be developed with minimal numbers of excipients. Below table indicates the commonly used excipients in direct compression formulation

Function	Common Examples
Diluent	Lactose monohydrate, anhydrous lactose, microcrystalline cellulose, partly pregelatinised starch, mannitol, dibasic calcium phosphate (anhydrous &dihydrate)
Disintegrant	Croscarmellose sodium, sodium starch glycolate, crospovidone, partly pregelatinised starch, low substituted hydroxypropyl cellulose
Lubricant	Magnesium stearate, calcium stearate, sodium stearyl fumarate, stearic acid
Glidant	Colloidal silicon dioxide, talc
Pigment	Aluminium lakes, iron oxides
Stabiliser	Buffers such as sodium carbonate and citric acid. Antioxidants such as butylated hydroxyanisole and butylated hydroxytoluene
Surfactant	Sodium lauryl sulphate, polysorbates

Since maximum herbal extracts including senna extract are hygroscopic, the direct compression method is considered to be appropriate. Sennosides A & B were compatible with a wide variety of powdered excipients. However, these were incompatible with propyl paraben, sodium carbonate,

stearic acid, citric acid, PEG, and sugar derivatives such as lactose, glucose and sorbitol when granulated with water[18].

For development of fast disintegrating formulation of senna following excipients were selected due to its advantages over other excipients. Microcrystalline cellulose and dibasic calcium phosphate are very commonly used diluents in tablet, which are available in grades especially suited to direct compression. 60% of top US prescription drugs contains microcrystalline cellulose as one of the excipient.

Dibasic calcium phosphate have a good compaction properties, and the good flow properties. Mannitol is another excipient used as diluent in direct compression formulations, due to its hydrophobic nature, suitable for moisture-sensitive active ingredients.

To formulate a fast disintegrating tablet a super-disintegrant that can effectively disintegrate a tablet when used at low concentrations (2-6% by weight) is preferred. Sodium starch glycolate is commonly used super-disintegrant in tablet formulation.

Colloidal anhydrous silica is used in the formulation as a glidant at a typical level of 0.1-1.0% to improve the flow characteristics of a compression mix.

Magnesium stearate is used in the majority of direct compression tablets and is more effective lubricant than talc, stearic acid etc.

Pre-compression Parameters

An optimum flow of powder must be achieved to ensure uniform feed from hoppers into dies and for achieving reproducible tablets with acceptable content uniformity, weight variation, and physical consistency. Due to their inherent heterogeneity and segregation tendencies of herbal powder during processing and handling, it is difficult to predict their behavior. The flow properties of the powder blend was analyzed before compression to tablets and the powder blends were indicated a good free flowing property which where within prescribed limits. The results of pre-compression parameters are given in Table 2.

Table 2: Pre-compression studies of powder blend

Formulations	Bulk density	Tapped density	% Compressibility	Hausner's ratio
F1	0.520	0.609	14.583	1.171
F2	0.461	0.579	20.37	1.255
F3	0.490	0.682	28.169	1.392
F4	0.436	0.599	27.143	1.372
F5	0.459	0.622	26.250	1.356
F6	0.468	0.587	20.272	1.255

Physical Parameters

Fast disintegrating tablets of senna extract were formulated by using superdisintegrants in different ratio. The results of post compression parameters are summarized in Table 3. Herbal dry extracts mainly due to their hygroscopic nature, increase the tablet hardness and prolong the disintegration time. As the tablet powder blend was free flowing (F2-F6 formulation), tablets produced were of uniform weight with acceptable weight variation in the range of 246 to 254 mg due to uniform die fill. Uniform thickness was found for all formulations and which is in the range of 3.98-4.20 mm. The hardness of each batch was evaluated and it was more than 27.0 N. Friability for F2-F6 formulation was found between 0.21-0.31% which indicate the tablets had a flair mechanical resistance. From the results of distintegrating study it was observed that the formulation F6 with 13 mg of sodium starch glycolate disintegrates within 45 sec and better release rate with mean 100.1% at 120 min than other formulations. Fast disintegration of tablets leads to quick dissolution and rapid absorption which may produce rapid onset of action[19]. Hence F6 formulation considered to be desired formulation and it has been taken for further stability study. Heavy metal and microbial count in the formulation largly depends on selection of excipients. Special emphasis were given while selecting the excipients which have less heavy metal concentration and microbial load. The heavy metal content was determined by AAS (Fusion scientific Lab & Charak testing Lab, Mumbai), the results complies to standards of heavy metals as per WHO (Table 4). The compressed tablets were analyzed for microbiological purity and results are complying to pharmacopoeia limit (Table 5)[20].

Table 3: Post compression parameters of senna tablets

Formulations	F1	F2	F3	F4	F5	F6
Drug content % (Assay)	98.4	99.4	99.1	98.9	98.5	99.9
Weight variation (%)	>5%	>2%	>2%	<1%	<2%	<2%
Thickness (mm)	4.05-4.20	4.15-4.20	4.15-4.20	3.98-4.08	3.98-4.02	3.87-3.91
Hardness (N)	27-40	37-52	40-45	40.15-54.50	38.94-45.25	36.24-51.54
Friability (%)	1.09	0.31	0.31	0.26	0.21	0.26
Disintegration Test	22.0 min	3.0 min	6.0 min	2 min 38 sec	2 min 18 sec	45 sec
Dissolution (As per USP)	97.6	97.5	97.4	97.1	98.0	100.1

Table 4 - The heavy metal content of senna tablets

Heavy metals	WHO and AYUSH limits	Observed in formulation (ppm)
Lead (Pb)	NMT 10 ppm	0.5
Mercury (Hg)	NMT 1 ppm	0.02
Arsenic (As)	NMT 3 ppm	2.0
Cadmium (Cd)	NMT 0.3 ppm	0.025

NMT: Not more than

Table 5: Microbiological purity initial and after 6 months stability study

Sr. No	Microbial Count (cfu/gm)	Pharmacopoeial Limit	Initial	6 Months
1	Total Aerobic Microbial Count	NMT 1000	110	25
2	Total combined Yeasts/Moulds	NMT 100	10	10
3	count	Should be absent	Absent	Absent
4	*Escherchia coli*	Should be absent	Absent	Absent
5	*Salmonella*	Should be absent	Absent	Absent
6	*Pseudomonas aeruginosa*	Should be absent	Absent	Absent
7	*Staphylococcus aureus*	NMT 100	Absent	Absent
8	Bile tolerent gram negative bacteria Clostridium spp.	Should be absent	Absent	Absent

NMT: Not more than

Stability Study

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light, and enables recommended storage conditions, re-test periods and shelf lives to be established. Microbiological purity was analyzed after 6 months accelerated stability and the results are complying to pharmacopoeial limit.

CONCLUSION

In the present study a successful attempt was made to formulate fast disintegrating tablets of senna extract for immediate release. The formulated tablets showed compliance for various physiochemical parameters along with dissolution as per USP, microbiological purity and heavy metals limit laid down by WHO. The stability results confirms that the direct compression approach with appropriate excipients is suitable for formulation of preservative free herbal tablets. In future, clinical studies are required to prove it effectiveness after fast dissolution and also need to develop a new drug delivery formulation like orodispersible/ mouth dissolving tablets.

REFERENCE

1. Solomon R, Golusu B, Devathi SK, et al. Herbal plant *Cassia angustifolia*. Jamonline, 2011, 1(1), 1–5.
2. http://www.drugs.com/npc/senna.html.
3. Das PN, Purohit SS, Sharma AK, et al. A Handbook of Medicinal Plants. Agrobios 2003;118.
4. Martindale, The Extra Pharmacopoeia, 31st ed., London. Royal Pharmaceutical Society 1996; 1240.
5. De Witte P, Lemli L. The metabolism of anthranoid laxatives. Hepatogastroenterolog 1990;37: 601-605.
6. Patent: Assessmetn report on cassia senna Land cassia angustifolia Vahl, folium.

http://www.ema.europa.eu/docs/en.GB/document_library/Herbal_-_HMPC_assessment_report/2009/12/WC500018219.pdf.

7. Surekha V, Thiruvengada R, Chetty CM. A review on determination of preservatives in food stuffs by different analytical methods. Pharmatutor. 2008.
8. Directly compressible high load acetaminophen formulations, WO 1997017947 A1.
9. Chan K, Some aspects of toxic contaminants in herbal medicines. Chemosphere. 2003, 52, 1361-1371.
10. Chan TY, Chan JC, Tomlinson B, Critchley JA, Poisoning by Chinese herbal medicines in Hong Kong: A hospital-based study. Veternary and Human Toxicol. 1994, 36, 546-547.
11. Saper RB, Kales SN, Paquin J, Burns MJ, Eisenberg DM, Davis RB, Heavy metal content of ayurvedic herbal medicine products. JAMA. 2004, 292, 2868-2873.
12. Saper RB, Phillips RS, Sehgal A, Khouri N, Davis RB, Paquin J, Lead, mercury, and arsenic in US-and Indian-manufactured Ayurvedic medicines sold via the Internet. JAMA. 2008, 300, 915-923.
13. Singh S, Shah D, Development and characterization of mouth dissolving tablet of Zolmitriptan. Asian Pac J Trop Dis. 2012, S457-S464
14. Patel P, Roy A, Vinodkumar SM, kulkarni M, Formulation and evaluation of colon targeted tablets of ornidazole for the treatment of Amoebiosis. Int J Drug Devel Res. 2011, 3(1), 52-61.
15. Agarwal V, Bhattacharya A, Bajpai M, Preformulational and delayed release formulation study on Senna leaf powder and Calcium sennoside. J Pharm Res. 2011, 4,7, 2245-2249.
16. Ali M, El-hassan, Shayoub ME, Abdalkreem MA, Osman HM, Khalifa K, Design, formulation, and evaluation of senna effervescent tablets. J Forest Prod Ind. 2012, 1(2), 21-25.
17. Singh S and Singh J. Development of accelerated stability protocol for sildenafil tablets – A European perspective review. Int J Pharma Bio Sci. 2010, 1(4), 27-34.
18. Quintin Verloop, , Wilna L, Andries FM, Antonie PL, Melgardt MV. Compounded laxative formulations for substituting phenolphthalein with sennosides A & B in solid dosage forms. Trop J Pharm Res. 2004; 3 (1): 265-277
19. Velmurugan S, Sundar Vinushitha. Oral Disintegrating Tablets: An Overview. Int J Chem Pharm Sci. 2010, 1(2), 1-12.
20. Hina B, Rizwani GH, Naseem S, Determination of toxic metals in some herbal drugs through atomic absorption spectroscopy. Pak J Pharm Sci. 2011, 24(3), 353-358.