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Development of novel formulation technology for oral delivery of Sterculia Gum

Harshad KAPARE*[1], Sohan CHITLANGE [1] Kaveri AHER [1], Shivaji AHER [2]

[1] Dr. D.Y.Patil Unitech Society's, Dr. D.Y. Patil Institute of Pharmaceutical Science and Research, Pimpri, Pune, Maharashtra, India 4311018

[2] Sky Biotech Life Sciences Pvt. Ltd., Georai Tanda, Aurangabad, Maharashtra, India 431001

*Corresponding Author. E-mail: hskapare@yahoo.in +91 8600839674

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ABSTRACT: Constipation and associated health issues like acid reflux, malnutrition were commonly observed in regions with water availability limitations. Although some of the products available in the market address this issue, there is limited research on development of such products which will be able to solve multiple associated issues. Sterculia gum, a natural product known for water retention and associated properties in traditional systems of medicine. Despite this, research and therapeutic applications of this product are in infancy. This study was aimed to develop laxative oral granules of sterculia gum with some other therapeutically and nutraceutical active ingredients for multiple applications as bulk laxative, demulcent, water retention agent, diarrhea and appetite controller in the management of obesity. Sterculia gum, magnesium trisilicate, dried magnesium sulphate, heavy kaolin and excipients characterization and product development was carried out with developed in house formulation technology. Developed formulation was evaluated for various formulation based evaluation parameters. Desirable pH range of 4.3 to 6.9 was observed indicating reduction in acidic properties of sterculia gum; good swelling index was observed 240ml/3gm. Identification tests and assay of active ingredients were carried and found to be within specified limit range. Developed formulation showed desirable stability of 12 months indicating good shelf life of product. Study results revealed developed formulation can be further investigated in clinical studies and might be served as novel dosage form for therapeutic applications in habitual constipation for multiple therapeutic targets with single product.

KEYWORDS: Granules; Constipation; Laxative; Nutraceutical; Sterculia Gum

1. INTRODUCTION

Gum exudates are some of the oldest natural gums. These have been used as thickening and stabilizing agents for over 5000 years. Sterculia gum, the primary exudate gum, serves a variety of purposes [1]. The 33rd Joint Expert Committees of Food Additives (JECFA/FAO) of 1988 defines Sterculia Gum, a dried exudation from the stems and branches of *Sterculia urens Roxburg* and other species of Sterculia (Fam. *Sterculiaceae);* consist mainly of high molecular-weight acetylated polysaccharides, which on hydrolysis yield galactose, rhamnose, and galacturonic acid, together with
minor amounts of glucuronic acid (Compendium of food additive specification, 2006). Sterculia gum has been recognized as Safe (GRAS) by the FDA following effective toxicological, teratological, and mutagenic studies. Literature also revealed that dietary Sterculia gum is neither digested nor degraded by enteric microflora, nor is it absorbed in any significant amount [1].

The Food and Agriculture Organization (FAO) has designed Sterculia gum as a food additive with the number E-416 since 1911 [2] and also given the read code y002J for its antidiarrheal activity, y08Cg for its bulk laxative activity, y00Gz for its appetite Suppressant's activity. Sterculia gum is synonymously known as

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Karaya, gum Karaya, Sterculia, gum Sterculia, in Hindi: Gulu, Kadaya, Karaya, Katera, Katilo, Kullo; Telugu: Tapsi (Compendium of food additive specification, 2006).

Sterculia gum is mostly found in tropical dry rocky hills and plateaus. *Bacterium Sterculia* gum is native to India and widely spread in the Indian region. It is mostly cultivated in Madhya Pradesh, Chattisgarh Their gum production is such a way that it can provide gum to half of India. It is also cultivated in Andhra Pradesh, Rajasthan, Gujarat, Odisha, Maharashtra, Karnataka and Tamilnadu. Sterculia gum production mostly takes place in the warmer months of April, May, and June. It is harvested by cutting the incissions of *Sterculia Urens Roxburg* tree in one square in size and after several days that area starts to exude gum and after 24 hours exudation gives large amounts of Sterculia gum. Then it is collected by villagers and sent to trading comporting agents who gave proper quantity to the quality products and packed in gunny bags and shipped to the communities. To improve the quality of gum, contaminants like bark, stem and foreign matter are separated by air floatation process. Because of air floatation process size reduction of gum takes place. To obtain homogenous product, it is passed through 6 to 30 # mesh size and those crystals and granules are used for bulk laxative properties [1-3].

Gum Karaya shows bulk forming property thus it is most commonly used as bulk laxative. It is soluble in water, due to its ability it swells into homogenous, creates adhesive and form a mucilaginous gel when exposed to water. It is partially insoluble in alcohol. It consists not less than 14% of volatile acid i.e., uranic acid, which is plant tissue associated with fibers, which are good to human and animals thus it is called dietary fibers. It is mostly found in mucilage. These granules have the ability to absorb to 70-100% of their original size. Gum Karaya is sometimes used as a laxative and for diverticular disease. Osmotic aids are often provided by gum, which can be obtained from powder, paste, a ring, a disc, or a sheet of paper. Sterculia [1-3].

Acid reflux due to constipation is a common condition. Heavy meal, spices, excess consumption of meal, beef, etc. which develop constipation by causing accumulation of hard stool in lumen, which obstruct the outflow of acid in stomach and also because of continuous administration of muscle relaxant or blood pressure medicine, which causes acidity [4-8]. Formulation containing Sterculia gum helps by absorbing water in the intestine and creates bulk and more liquid like stool which gives relief from constipation [9] and acidity issue can be controlled by co-administration of Magnesium Trisilicate as an antacid [10-11]. Dried Magnesium Sulphate and Sterculia gum retain water in the body for a full day, reducing discomfort associated by irritation in stomach and acidic condition due to decrease in water content during fasting period [12-13]. In diarrhea conditions Heavy Kaolin gives relief from excess water loss [14-15] and 1% solution can prevent heat stroke by retaining water for a longer period of time [16-18]. Most of the country areas where water percentage is less; this formulation may help by maintaining the water concentration in the body for a longer period of time [18-22].

Magnesium Trisilicate is a common antacid drug that is used for the treatment of gastro esophageal reflux. It is also used as an antioxidant, decolorizing agent and industrial odor absorbent [10]. Dried Magnesium Sulphate the supplement acts as osmotic laxative, which means it relaxes bowel and pulls water into intestines. Water helps soften and bulk up stool, which makes it easier to pass. It also increases the content of non-digestible and absorbable material in the colon [12-13]. Heavy Kaolin is a natural adsorbent anti-diarrheal agent that has been used as adjuncts to rehydration therapy in the management of diarrhea [14-15].

As per market research study, there are limited such formulations available as laxative but due its composition these are having limitations in terms of acidity or formulation parameters associated issues. To overcome these issues in proposed formulation magnesium trisilicate is incorporated as an antacid. Apart from this developed formulation was designed with nutraceutical potential for ease of regular administration by considering situations of nutraceutical requirements of certain region worldwide.

2. RESULTS AND DISCUSSION

Laxative oral granules were observed to be light orange brown in color with pleasant odor. Granules showed 0.9ml of bulk volume per gram of granules, 1gm/ml of tapped density which is suitable for unit dosage packaging. Carr' index, Hausner's ratio and angle of repose were observed to be 10%, 1.1 and 28° respectively, which reveals excellent flow properties of granules. 240ml/ 3gm swelling index was observed for the finished product.

Table 1: Physical characteristics of finished product Sterculia gum granules

Sr. No.	Parameter	Value
1.	Color	Light brown-colored granules
2.	Odour	Pleasant odor
3.	Bulk density	0.9 ± 0.02 gm/ml
4.	Tapped density	1± 0.03 gm/ml
5.	Carr's Index	10%
6.	Hausner's Ratio	1.1
7.	Angle of repose	28°
8.	Swelling Index	240± 0.2 ml/3gm

2.1 Analysis of Finished product

Analysis of the finished product was carried out and parameters were summarized in Table 2. Laxative oral granules were found to be sparingly soluble in water and swells in homogenous, adhesive and gelatinous mass. Finished product showed a change in pH range from 4.3 to 6.3 that indicated reduction in acidic property of Sterculia gum. Formulation granules appeared as translucent, angular particles and stained particles of granules when mounted in ruthenium red indicates presence of Sterculia gum in the formulation. Formulation is not intensely colored than solution of methylene blue confirms the presence of heavy kaolin in the formulation.

Total ash value was observed 27.6 % ± 0.5 %and volatile acid 19.0 % + 0.8 % which are within the limit range (NLT 40%). Drug content of magnesium trisilicate 98.32 % ± 0.7 % and magnesium sulphate 98.55 % ± 1.1 % were observed within the limit range (NLT 90%).

Table 2: Finished product specifications for Sterculia gum granules

Tests	Results
Solubility	Sparingly soluble in water but swell in 3 gm of homogenous, adhesive, gelatinous mass. Practically insoluble in ethanol (96%). Sterculia gum granules when added in 240 ml, tacky and viscous granular mucilage are produced after 24 hours. Figure:3 (a)
pH	Change pH 4.3 of Sterculia gum to pH 4.3 to 6.9 of Sterculia gum granules. Figure:3 (b)
Identification	
Sterculia Gum	Appears as a small transparent, angular particle of various sizes & shapes. With granular mucilage is produced. Figure:3 (c) Particles are stained red when mounted in ruthenium red solution Figure:3 (d)
Heavy Kaolin	Solution is not intensely coloured than solution of methylene blue. Figure: 3 (e)
Total Ash	27.6 % +0.5 % (NMT 30%)
Volatile Acid	19.0 % +0.8% (NLT 14%)
Assay	
Magnesium Sulphate	98.32 % +0.7 % (NLT 90%)
Magnesium oxide	101.55 % +1.1 % (NLT 90%)

2.2 Spectral Characterization

Fig. 1 B spectra of Magnesium Trisilicate showed rocking mode with broad & shallow absorption band of $Si\text{-}O^-$ at $509cm^{-1}$. Symmetric mode with broad absorption bond at $657.75\ cm^{-1}$ of Si-O-Si. Stretching vibration of $Si\text{-}O^-$ found at $1464.02cm^{-1}$. Fig. 3 C spectra of Dried Magnesium Sulphate showed absorption bond at $1639.55cm^{-1}$ indicates bending mode of vibration in H-O-H and the broad and shallow bond observed in the region between $3000cm^{-1}$ to $4000cm^{-1}$shows the stretching mode of vibration of OH group and also shows the formation of MgO. Fig. 3 D spectra of Heavy Kaolin showed the deformation of Al-O-Si at $560.59cm^{-1}$, deformation of Si-O-Si at $522cm^{-1}$, OH deformation of inner surface at $965.6cm^{-1}$ and $1637.62cm^{-1}$ of water. OH stretching is observed at $3423.76cm^{-1}$and $3626.94cm^{-1}$. Fig. 3 E of finished product sample spectra shows the presences of Si-O-Si symmetric mode at $634.60cm^{-1}$, $Si\text{-}O^-$ stretching mode at $1111.03cm^{-1}$ and rocking mode at $499.58cm^{-1}$. Al-O-Si bond observed at $789cm^{-1}$, along with in between $400cm^{-1}$ to $600cm^{-1}$ Al-O-Si bond is observed. Absorption from $3000cm^{-1}$ to $4000cm^{-1}$ showing MgO and vibration of OH. OH deformation is found at $1722.43cm^{-1}$ and stretching is observed at $3433.56cm^{-1}$ and $3612.79cm^{-1}$.

2.3 Stability Study

Developed formulation showed that formulations were stable in terms of various evaluation parameters up to 12 months within acceptable limit as shown in table 3.

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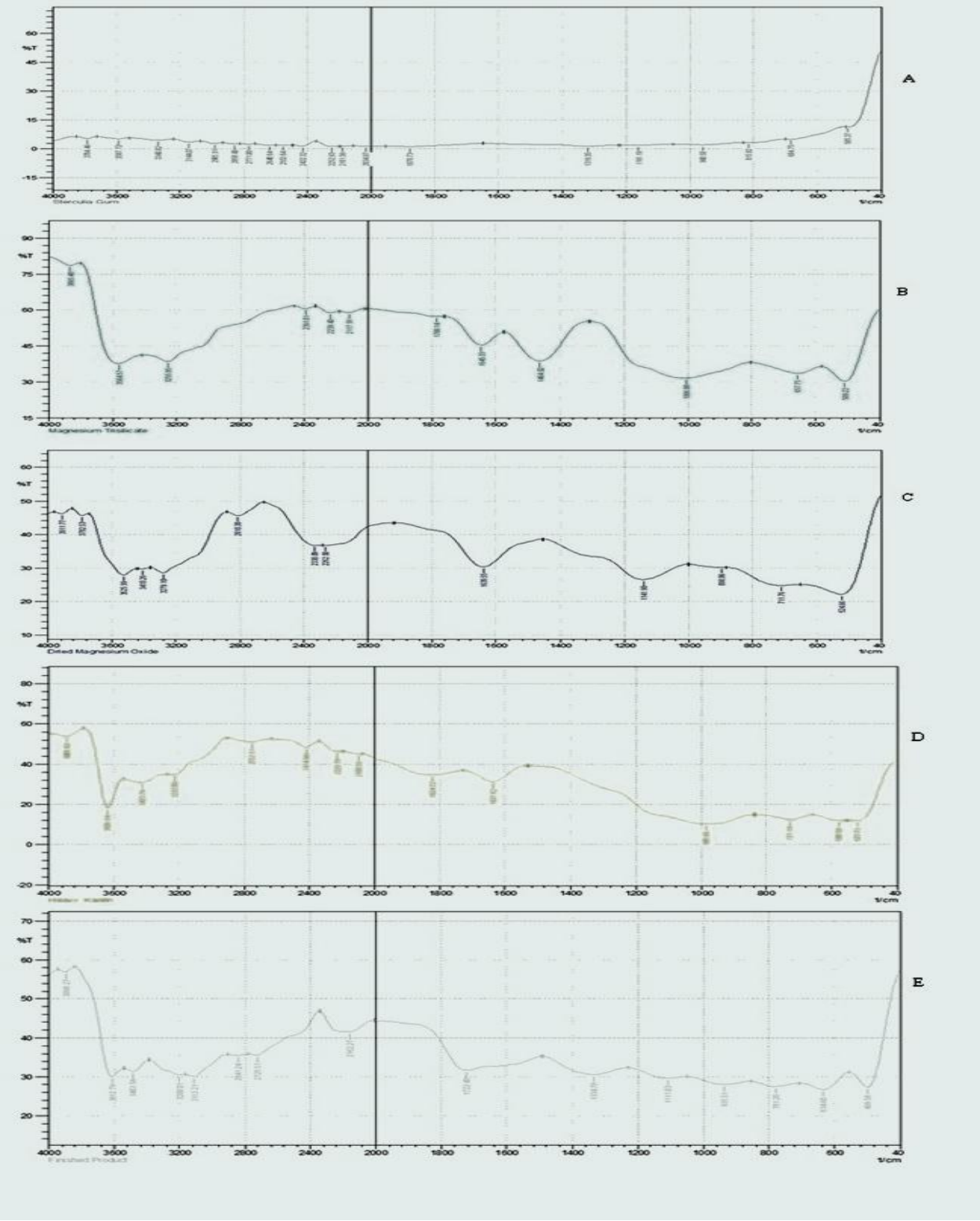

Figure 1. FTIR spectrum of A. Sterculia Gum, B. Magnesium Trisilicate, C. Dried Magnesium Sulphate, D. Heavy Kaolin, and E. Finished Product Sterculia Gum Laxative Granules

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Table 3: Accelerated Stability study (n = 3)

Test	Specification	Batch no.	Initial	After 3 months	After 6 months	After 9 months	After 12 months
Description	Light brown coloured granules with pleasant odour	A	Complies	Complies	Complies	Complies	Complies
		B	Complies	Complies	Complies	Complies	Complies
		C	Complies	Complies	Complies	Complies	Complies
Identification of Sterculia gum	As per Specified procedure	A	Complies	Complies	Complies	Complies	Complies
		B	Complies	Complies	Complies	Complies	Complies
		C	Complies	Complies	Complies	Complies	Complies
Identification of Heavy Kaolin	As per specified procedure	A	Complies	Complies	Complies	Complies	Complies
		B	Complies	Complies	Complies	Complies	Complies
		C	Complies	Complies	Complies	Complies	Complies
pH	Between 5.0 to 7.0	A	5.97 +0.2	5.82 +0.4	5.75 +0.3	5.75 +0.2	5.73 +0.4
		B	6.04 +0.3	5.96 +0.3	5.92 +0.3	5.90 +0.4	5.89 +0.2
		C	6.02 +0.2	6.0 +0.2	5.94 +0.2	5.98 +0.4	5.97 +0.4
Volatile Acid	NLT 14 %	A	17.5%+0.3	17.29%+0.3	16.93%+0.3	16.89%+0.3	16.83%+0.2
		B	17.7% +0.4	17.58%+0.3	17.20%+0.2	17.29%+0.2	17.75%+0.3
		C	17.77%+0.2	17.69%+0.2	17.30%+0.3	17.73%+0.2	17.84%+0.2
Assay of Magnesium Sulphate	NLT 90% of label claim	A	100.13%+1.3	101.81%+1.1	99.94%+1.2	100.10%+1.2	99.8% + 1.6
		B	102.01%+1.3	101.81%+1.4	101.81%+1.4	100.06%+1.3	99.8% + 1.4
		C	102.14%+1.2	100.51%+1.2	101.81%+1.4	100.03%+1.2	99.72%+1.2
Assay of magnesium oxide	NLT 90% of label claim	A	102.30%+1.1	101.94%+1.3	101.44%+1.2	100.36%+1.2	100.51%+1.4
		B	101.45%+1.0	101.24%+1.3	100.74%+1.4	100.20%+1.4	100.25%+1.3
		C	101.55%+1.2	101.4% + 1.2	100.83%+1.2	100.15%+1.4	100.45%+1.4

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3. CONCLUSION

Sterculia gum oral laxative granules as a product based on hypothesized concept containing magnesium trisilicate as an antacid, dried magnesium oxide as osmotic laxative and heavy kaolin with anti-diarrheal effect was formulated with novel in house developed technology-based approach for oral administration. Formulation characterization parameters were observed within the specified range of finished product specification based on physiological and formulation requirements. This novel formulation might be useful with further clinical trials investigation for patients suffering from constipation, acid reflux, diarrhea, along with nutraceutical, appetite management, etc.

4. MATERIALS AND METHODS

4.1 Materials

The Sterculia gum collected in the month of March was purchased from gum keeper Shivam Enterprises from Madhya Pradesh, India. Magnesium Trisilicate was purchased from LOBA Chemie laboratory reagents. Heavy Kaolin and Dried magnesium Sulphate was purchased from Sciencelab.com, Inc. Chemical laboratory equipment from the Houston region of Texas. All reagents used were of analytical grade from Merck, India. All this material is obtained from the store department of SKY Biotech Life Sciences, Pvt Ltd, Aurangabad, Maharashtra, India

4.2 Material Characterization

Characterizations of active ingredients and excipients were carried out according to British Pharmacopoeial 2020 specifications. Microbial Contamination study of Sterculia gum, Magnesium Trisilicate, Dried magnesium Sulphate, Heavy Kaolin was carried out by performing test of total viable count, total bacterial count, total fungal count along with test for *Escherichia coli*, *Salmonella*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* [23, 26-29].

4.3 Formulation development

Initially formulation development was carried out with trial batches with developed process and on basis of primary evaluation final batch was optimized as per below formula for 100 gm granules:

Table 4: Composition of Sterculia Gum Laxative Granules.

Sr.No.	Ingredients	Role	Quantity (gm) per 100 gm batch
		Active Pharmaceutical Ingredients	
1.	Sterculia Gum	Laxative	60.00
2.	Magnesium Trisilicate	Antacid, Gastroesophagal reflux	0.10
3.	Dried Magnesium Sulphate	Osmotic Laxative	3.70
4.	Heavy Kaolin	Adsorbent, Anti-diarrheal	20.00
		Excipients	
5.	Talc	Lubricant	6.461
6.	Sucrose	Sweetener	6.124
7.	Arabic Gum (Acacia Gum)	Coating Agents	2.628
8.	Chlorophyllin Cupric	Chelating Agents	0.014
9.	Vanillin	Flavoring Agents	0.069
10.	Sunset Yellow Color	Coloring Agents	0.900

4.4 Formulation Methodology

4.4.1 Step I: Preparation of Sterculia gum granules

Sterculia gum was added on mechanical vibratory sifters (14#). Granules were collected from polythene line HDPE containers and labeled the container with batch details. Fine particles were passed and discarded through 14# screen. Further granules were dried at 40°C in the FBD. It helps to reduce the size of the granules and make granules dry by reducing water by about 30%. After drying it was sieved with 14# to obtain uniform size granules. Uniform size reduces 30 % mass of the water. Further granules were kept for 3 hours in the pan at 70°C for again reduction of moisture content.

4.4.2 Step II: Preparation of coating powder

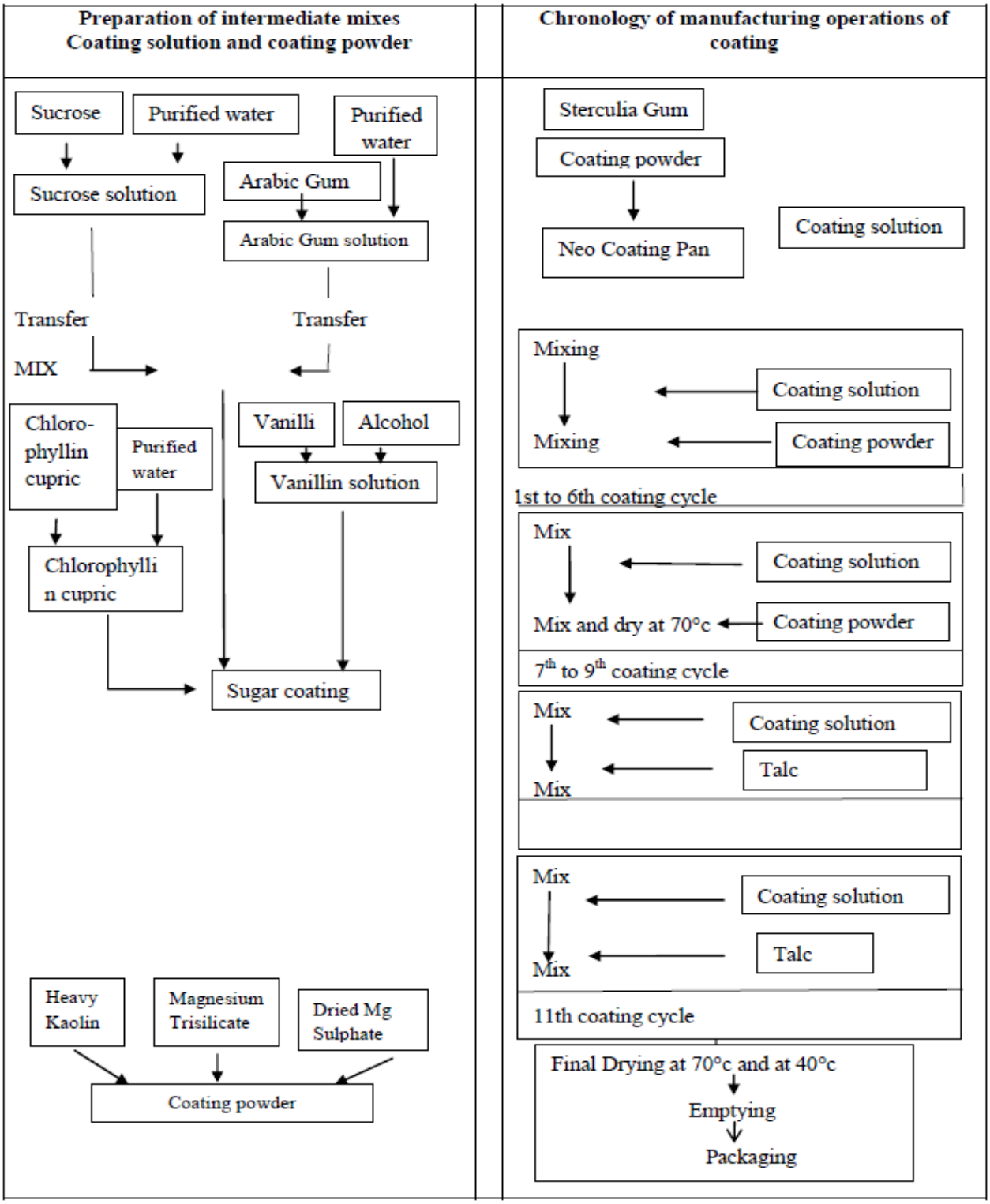
Magnesium Trisilicate BP, Dried magnesium oxide and heavy kaolin were weighed and sifted with 40# size on vibratory shifter. Sifted material was mixed in an octagonal blender for 15 min.

4.4.3 Step III: Preparation of coating solution

Coating solution was prepared by using a stainless-steel reactor with agitator assembly. Three-liter purified water was added in Gum Arabic under continuous stirring slowly till it completely dispersed. Three-liter water is boiled separately and sugar was added into boiled water & allowed it to completely dissolve. Solution was filtered through the 200 # nylon cloth in clean S.S. vessel. Then hot sugar syrup was added into Gum Arabic solution in hot condition and stirred until a homogenous mixture was formed. Chlorophyllin cupric BP was dissolved in 120 ml purified water and added into the above homogenous mixture. Vanillin solution is prepared by dissolving vanillin in Isopropyl alcohol and then vanillin solution is added to sugar coating solution. Sunset yellow color was dissolved in purified water and added to sugar coating solution, stirred it for 20 min. kept this solution at 60°C throughout coating process

4.4.4 Step IV: Coating

Neo Coater Pan is loaded with Sterculia gum for sugar coating. Bed was maintained to warm about 50°C to an inlet temp of 50°C throughout the coating process. Coating solution in lots of approx. 200-250ml was spread over granules at a time under pan speed of 15 rpm. Further pan speed was reduced at about 9-10 rpm and incorporated about 450 gm powders to spread uniformly on the wet bed gum. First to sixth coating cycles were performed by maintaining the temperature of the coating pan about 70°C. Bed was allowed to dry completely before the next coat. Coating cycles were continued till the coating powder completely coated on the gum. Total 11 cycles were given to complete the coating of granules. Further coating of talcum was done with the same process. After completion of the process all coated granules were dried at 70° for 15 min. (Scheme: Manufacturing Operation, Fig. 2 and 3)



Scheme: Manufacturing Operation

Figure 2. Raw Sterculia Granules (standard)., Appearance of granules after 6th cycle, 9th cycle, 10th cycle and 11th cycle of coating, Finished product of oral laxative Sterculia Gum Granules.

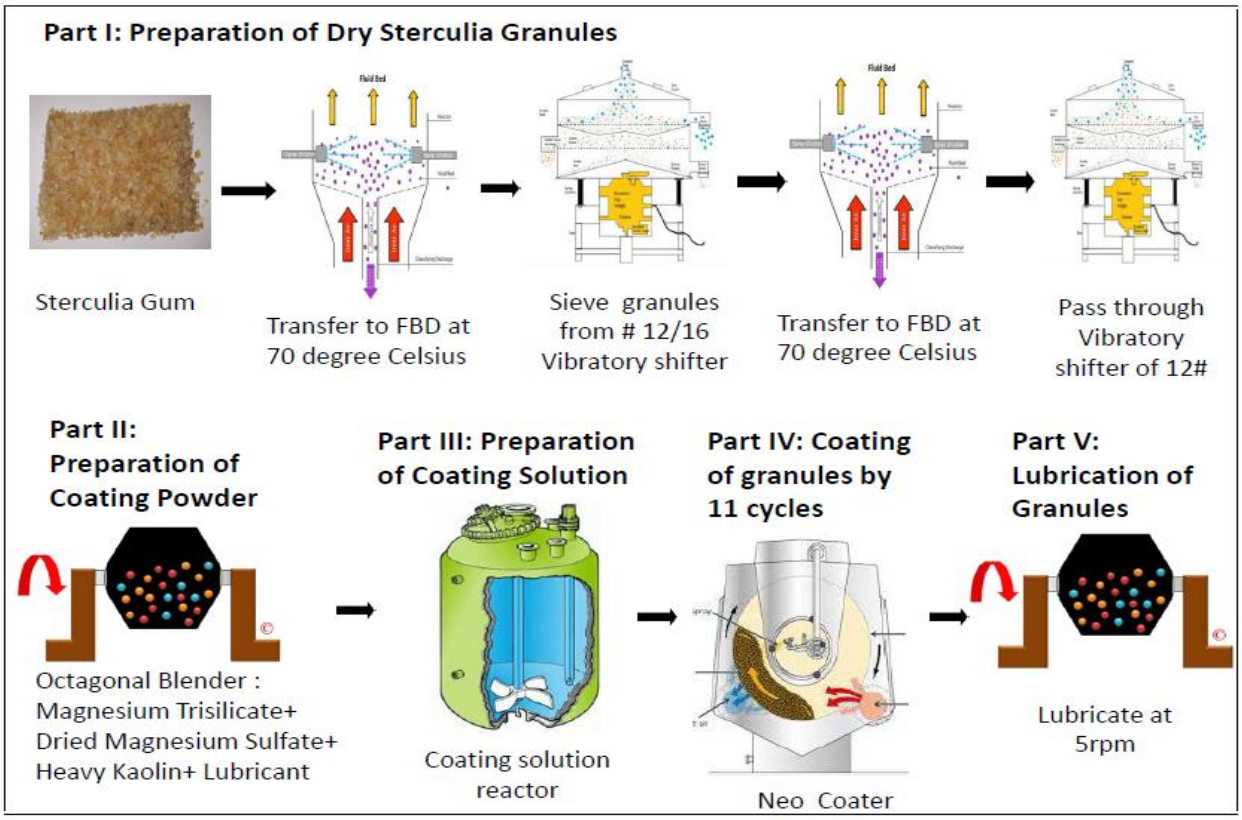


Figure 3. Manufacturing Process of Sterculia Gum Laxative Granules

4.5 Evaluation of finished product

Physical appearance of the finished product was observed In terms of color, odor and appearance. Various granules parameters were evaluated in terms of its bulk Density, tapped Density, Carr's Index, Angle of repose etc. were evaluated to determine flow properties [23, 24]. The swelling Index was determined as per specification. Swelling index is the volume in ml occupied by 1gm of drug; including any adhering mucilage after it has swollen in an aqueous liquid for 4 hr. One gm of formulation was taken in a 25mL glass stopper cylinder graduated over a height of 120 to 130 mm in 0.5 mL divisions. About 25 mL of water is added and shaken vigorously every 10 minutes for 1 hour and allowed to stand for 3 hours. The volume occupied by the formulation including adhering mucilage was measured.

4.6 Identification tests

4.6.1 Sterculia Gum B.P.:

Sample was powdered and mounted in ethanol (96%) it appears as small, transparent, angular particles of various sizes and shapes; the water was added, particles lose their sharp edges and each gradually swells until a large, indefinite, almost structure fewer mass results; further it was mounted in ruthenium red solution the particles are stained red; no blue colored particles (starch) are visible when mounted in iodine solution. 1gm was added to 80 mL of water and allow standing for 24 hours, shaking occasionally. Tacky and viscous granular mucilage is produced. Mucilage was retined for use for further study. 4 mL of mucilage was boiled with 0.5 mL of hydrochloric acid, add 1mL of 5M sodium hydroxide, and add 3ml of cupric-tartaric solution to the sample and heated which produces red precipitate. Further warm 0.5 g with 2mL of 5M sodium hydroxide, brown color was produced (25,26).

4.6.2 Heavy Kaolin:

In a ground glass stopper test tube 0.1 gm of sample was shaken with 10 ml of 0.37% w/v solution of methylene blue for 2 minutes and allowed to settle. Further sample was centrifuged and diluted 1 volume of solution to 100mL volume with water. The solution was compared for color intensity with 0.003% solution of methylene blue (25, 27).

4.6.3 Magnesium Sulphate:

Sterculia gum sample equivalent to 0 .032 g of magnesium sulphate was dispersed in 20 ml of dilute hydrochloric acid and diluted up to 100.0mL with distilled water. Further Allowed it to stand for an hour and then this solution was filtered through 100 # sieve. This filtrate was taken for complexometric titration of magnesium Sulphate. This sample solution was taken into a 500 mL conical flask and diluted to 300mL with distilled water. 10 mL of ammonium chloride buffer solution pH 10.0 was added. 50 mg of mordant black 11 triturate was used as an indicator. Above solution was heated to about 40°C then titrated with 0.05 M sodium edetate until the color changed from violet to colorless (28).

4.6.2 Magnesium oxide:

1gm of sample was taken in 200 mL conical flask, 35mL of hydrochloric acid and 60 mL of distilled water was added. Above solution was heated in water bath for 15 minutes. Further it was allowed to cool, filtered and washed conical flask and residue with distilled water. Further it was diluted and washed again with 250 mL of distilled water. 50 mL of above solution was neutralized with strong sodium hydroxide solution and titrated with 0.1 M sodium acetate solution (29).

4.7 pH

Powdered Sterculia Gum granules sample equivalent to 1.0g Sterculia Gum was added to 80mL of water and allowed to stand for 24 hours, with occasional shaking. Tacky and viscous granular mucilage was produced. pH was measured at 25°C+ 2°C using a calibrated pH meter.

4.8 Total Ash

Silica crucible was ignited at 600°C ± 50°C for 30 min; and allowed to cool in a desiccator over silica gel and weighed (W1). Powdered Sterculia granules sample equivalent to 1.0 g Sterculia Gum was placed in the crucible and weighed the crucible with the contents (W2). Further crucible was heated gently until white fumes no longer evolved and ignited at 600°C ± 50°C until the residue was completely incinerated. Further crucible was allowed to cool in desiccator over silica gel, weigh it again (W3) and percentage of residue amount was calculated.

4.9 Volatile Acid

Powdered Sterculia granules sample equivalent to 1.0gm Sterculia gum was transferred in 700ml Kjeldahi flask, 100 mL of distilled water and 5 mL of orthophosphoric acid was added and allowed it to stand for 3 hours until the gum was completely swollen. Further it was boiled under a condenser for 2 hours. This content was transferred to 1000mL round bottom flask, and rinsed Kjeldahi flask with 800 ml of distillate. Acid residue measures about 20 mL and titrated the distillate with 0.1M sodium hydroxide against using phenolphthalein solution R1 as an indicator. Procedure was repeated without the substance being examined. The difference between the titration represents the amount of alkali required to neutralize the volatile acid. Each mL of 0.1M sodium hydroxide verses is equivalent to 6.005mg (0.006005g) of volatile acid, calculated as $C_2H_4O_2$.Limit: Not less than 14.0% calculated as acetic acid, $C_2H_4O_2$

4.10 FTIR Spectroscopy

The FT-IR studies of Sterculia Gum, Magnesium Trisilicate, Dried Magnesium Sulphate, Heavy Kaolin and finished product were carried out using Shimadzu 8400S. The baseline correction was made using dried potassium bromide (KBR). The sample 2-3 mg was mixed with the potassium bromide to obtain uniform dispersion. The dispersion was kept in a sample cell which was fitted on the sample holder and the spectrum was recorded in the range of wave number acquired was from 400 to 4000 cm^{-1}. The spectra were used to identify the major Functional group and to determine any possible interaction of the formulation components. (Figure 1)

4.11 Stability Study

Sterculia gum granules of 3 batches: A, B, C of 100gm sample were subjected to stability study according to ICH Q1A guidelines at accelerated ambient temperature of 40°C ± 2°C with Humidity 75% RH ± 5%RH for 12 months. Finished product parameters including description, identification of Sterculia gum and heavy kaolin; pH; volatile acid; assay of magnesium Sulphate and magnesium Trisilicate were evaluated for determination of stability of finished product. (Table 4)

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