

Formulation And Evaluation of Nutraceuticals Using Poly-Herbal

Srushti Gode*, Sanket Dharashivkar, Kamlesh Soni, Rini Punathil, Aniket Gudur, Neha Ghosalkar

Department of Pharmaceutics, St. Wilfred's Institute of Pharmacy, Panvel

ABSTRACT

With the increasing incidence of diabetes mellitus, to have a hypoglycemic effect, interest in plant-based nutraceuticals has increasingly grown. With the two extracts being polyherbal ethanolic ones of Litchi chinensis (lychee) seed and root of Withania somnifera (Ashwagandha) brought in for their antihyperglycemic action, the study focused on the formulation and evaluation of nutraceutical granules. Extraction was considered by maceration using ethanol as a solvent to retain a wide range of phytoconstituents. Preliminary phytochemical screening revealed the presence of alkaloids, flavonoids, tannins, glycosides, and saponins as bioactive constituents. Alkaloids, flavonoids, tannins, glycosides, and saponins are usually implicated in glucometabolic pathways. Thin Layer Chromatography (TLC) was performed to check for compound diversity and FTIR was used to detect functional groups. Granules were prepared by the wet granulation process followed by characterization for critical physicochemical properties such as angle of repose, bulk and tapped density, Carr's index, Hausner's ratio, and moisture content. Values found for all the parameters from the various testing methods were within the limits described in the standard pharmacopoeias, thus indicating that the formulations exhibit good flow and compressibility characteristics and are suitable for oral administration. The combination of lychee seed and Ashwagandha extract offer a synergetic effect which may improve glucose metabolism as well as insulin sensitivity. The results suggest that the developed polyherbal nutraceutical granules have the potential hypoglycemic activity and may be used as a safe and effective supplement to manage hyperglycemia.

Keywords: Litchi chinensis, Withania somnifera, Hypoglycemic, Insulin sensitivity, Nutraceutical.

INTRODUCTION

In recent decades, herbs as one of the disciplines of NDDS have attracted considerable attention. Conventional dosage forms, especially prolonged-release dosage forms, fail to meet both supplying a drug component at a specific rate as required by the body and transporting phytoconstituents to the desired target site for maximized therapeutic response [1]. The modern drug distribution system is a new technique of delivering a drug apart from overcoming all the limitations associated with traditional drug delivery systems. Modern medicine cures a certain disease with a targeted treatment zone within a patient's body to directly reach the site of trouble and deliver the drug to that area. Drug delivery is the method of providing an optimum amount of drug to a patient in such a way that it reaches exactly the "site

of action" and starts upon therapy at that very instance. The new systems of conventional drug delivery try to eradicate all those disadvantages that are due to the conventional drug delivery systems. There are various approaches by which novel drug delivery can be achieved [2].

Nutraceuticals, which are functional foods or dietary supplements that provide health benefits aside from very basic nutrition, have received considerable attention in the past few decades. Granules, which are only one of the several types of nutraceuticals, have been in the spotlight for being the best choice so far because of their comfort of being used, being stable, and their possibility of controlled release of active drugs. Nutraceuticals are beneficial in a multitude of therapeutic areas such as cough and cold, treatment of arthritis, digestive disorders, sleep disturbances,

Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

cancer therapies, depression, diabetes, cholesterol, hypertension, and analgesics. The nutraceutical research and development sector are buzzing with activity to explore how different nutraceuticals will turn out to be beneficial in future medicines. Science is indeed demanding standardization of constituents for nutraceuticals as well as cautious formulation of protocol and undertaking clinical studies that might core to benefit consumer health and impact nutraceutical companies [3].

GRANULES:

The Latin word "granulatum," which names a granular mixture, comes from the same root as the English word "granulated." The word "granules" refers to the aggregation of small, fine particles in the pharmaceutical granulation process, which are subsequently developed into a bigger and more complex material. Among these structures, the average size is around 0.2 to 0.4 mm. "Usually, particles that are in the 0.2 to 0.5 mm range are created and then they are most effective for binding or pressing together during compaction. Pharmaceutical granulation, which is in a way, disperses the particles efficiently, already mentioned above, and is the key factor in the improvement of the medicine quality[4].



Figure 1 Nutraceutical Granules

Advantages Of Nutraceutical Granules [5]:

- 1) The dosage form of granules is most flexible and suitable for administration, especially for adult and child patients who have difficulty swallowing tablets or capsules.
- 2) Granules can be prepared by the dry granulation method or the wet granulation method.

- 3) Granules can also be coated or formulated for enteric or sustained release.
- 4) It is suitable for dispensing drugs in large dosages and is easy to take.
- 5) Granules are suitable for industrial production: the process is simple, with no need for punching or coating instruments at all.
- 6) Granules are also suitable in instances where the drug is sensitive to moisture because moisture is not involved in their formulation.

Limitations Of Nutraceutical Granules [6]:

- 1) Granules can be considered more uncomfortable for the patient to dispense and carry than tablets or capsules; hence this is seen as their main disadvantage.
- 2) Hygroscopic or deliquescent, amorphous, oxygen-sensitive, and volatile are among the types of APIs that are some of the most difficult to formulate.
- 3) To do granulation requires an expert in the process.
- 4) They require specific storage conditions; these drugs are stored in a dry place to inhibit moisture degradation.
- 5) Compared to tablets and capsules, granules may not necessarily prove to be in dosage form because they have a defined dose, greater precision, and lesser variability.
- 6) Granulation involves so many processing steps that consume great time, energy, and space, thus being an expensive technique.

The basic conceptual word for "Nutraceutical" was born around 3000 years ago. Hippocrates, the father of modern medicine, instigated this concept of a relationship between food for health and its therapeutic effect. Foods are meant to prevent disease or find cure for a disease. About 2,500 years ago, Hippocrates stated basically that, "Let food be your medicine and medicine be your food". Ancient writings and artworks of the Egyptians, Romans, and

Greeks disclosed the medicinal and spiritual application of plants.[7] During the past centuries, many sailors died of scurvy from long voyages. The body was examined, and the actual highlights of the lack of vitamin B and C in diet were present. Similarly, goiter turns common due to deficiency of iodine in salt. Around the start of the 20th century, US food manufacturers began the iodizing of salt for the prevention of goiter, which represents the first attempt at creating a functional ingredient by means of fortification.[8] Lychee (*Litchi chinensis* Sonn.) of the Sapindaceae family has *L. chinensis* ssp. *chinensis*, *L. chinensis* ssp. *Philippines's* (Radlk) Leenh, and *L. chinensis* ssp. *javensis* Leenh (Tindall, 1994; Liu et al., 2007) as its subspecies. Of all these subspecies, only *L. chinensis* ssp. *chinensis* is commercialized and cultivated. Lychee (*Litchi chinensis* Sonn.) is grown commercially in over 20 countries. Important lychee growing countries are China, India, Vietnam, Thailand, and South Africa [9]. This review article incorporates the nutritive composition of the litchi seed covering its phenolic compounds, bioactivity, and starchy polysaccharides (40.7%), proteins (4.93%), oil contents (3.2%), and minerals. It also opens the umbrella of bioactivities (anticancer, neuroprotective, antioxidant, antiviral, antimicrobial, hepatoprotective, lipid lowering) of the LSE. The amino acid profile of litchi seed proteins was said to possess all essential amino acids added by two uncommon amino acids that are α -methylenecyclopropylglycine (α -MCPG) and hypoglycin A (HGA). This limits the use of the seeds in the food industries due to their hypoglycemic effect in the human body [10].

Ashwagandha (*Withania somnifera*, fam. Solanaceae) is commonly known as "Indian Winter cherry" or "Indian Ginseng". One of the prime herbs in Ayurveda—an ancient system of medicine in India—used for millennia as a Rasayan for its very wide range of health benefits. Biologically active chemistries of *Withania somnifera* (WS) are alkaloids (isopelletierine, anafierine, cuseohygrine, anahygrine, etc.), steroidal lactones (Withanolides, withaferin), and saponins [11]. Ayurveda, an ancient Indian healing system having origins back to 6000 BC, is the parent from which all healing sciences have emerged. For at least the same 6000 years, Ashwagandha has been in use as a Rasayan, or an agent to increase one's

vitality in the life force. The Ashwagandha root is considered a tonic, aphrodisiac, narcotic, diuretic, anthelmintic, astringent, thermogenic, and stimulant. The root being perceived as having a horse-like smell ("Ashwa"), it was named Ashwagandha, suggestive of its imparting strength like that of a horse. It is employed essentially in emaciation of children (is an excellent tonic when given with milk to children) and residual debility conditions of old age, rheumatism, vitiated conditions of vata, leukoderma, constipation, insomnia, nervous breakdown, goiter etc [12].

MATERIALS AND METHODS

Materials:

This formulation includes some main ingredients, all serving a particular function. Lychee seed powder and Ashwagandha powder are the active pharmaceutical ingredients and were both purchased from the local market. Starch soluble, Lactose is diluted, supplied by Chemdyes Corporation, while starch, Polyvinyl Pyrrolidone (PVP K-30) is the binder. Crospovidone, Croscarmellose Sodium is an active disintegrant obtained from Alpha Chemika. From Sisco Research Laboratories Pvt. Ltd., Magnesium Stearate, Talc comes as a lubricant where talc is provided by Loba Chemie Pvt. Ltd and Magnesium Sterate is provided by Sisco Research Laboratories Pvt. Ltd. They also supply Methyl Paraben and Propyl Paraben as preservatives. Polyethylene Glycol 400 is use as Solubilizing agent which is supplied form the Sisco Research Laboratories Pvt. Ltd.

PROCEDURE FOR EXTRACTION

Maceration Extraction:

Maceration is a cold extraction method in which herbal materials in proper form are immersed in an appropriate solvent for a specified time to permit the active constituents to dissolve into the solvent. The 10 gm of dried powders of Ashwagandha roots and Lychee seed were weighed out accurately and placed into the 2 separate Conical flasks. After the addition of ethanol as solvent was added to the flasks. The flasks were tightly closed with the Aluminum foil so to protect from contamination. The extract was left to soak at room temperature for a period of 24-72 hours with occasional shaking during the soaking period. The liquid extract was then separated by filtration



method. After the water was evaporated off the filtrate, and the seed extract was obtained. As the extracts were profiled for the identification of active constituents within the plant samples had used [13].

Qualitative phytochemical screening

Aqueous extract of Ashwagandha was subjected to qualitative analysis of various active constituents, such as alkaloids, carbohydrates, Reducing Sugars, Proteins and Amino acids saponins, glycosides, Resins, Phenolic compound, Tannins, terpenoids, phenol, flavonoids [14].

Aqueous extract of Lychee seed was subjected to qualitative analysis of various active constituents, such as alkaloids, carbohydrates, Steroids, Terpenoids, glycosides, phenol, flavonoids [15].

Determination of calibration curve

1g of Ashwagandha powder was accurately weighed and dissolved in 100 ml of Distilled water, pH 7.4 in 100 ml of volumetric flask. The resulting solution had a concentration of 1 mg/ml (1000 µg/ml). From the prepared stock solution, 10 ml was further diluted to make up to 100 ml using PBS, pH 7.4 with concentration of 100 µg/ml. Different aliquots of 0.2 ml, 0.4 ml, 0.6 ml, 0.8 ml, 0.10 ml were diluted up to 10 ml with buffer. The absorbance of each solution was measured by UV-Visible spectrophotometer at

268 nm using PBS, pH 7.4 as blank. The graph of concentration versus absorbance was plotted [16].

Compatibility Study (FTIR)

Fourier Transform Infrared (FTIR) spectroscopy was performed to identify Ashwagandha and Lychee seed and analysis possible interactions between the drugs and excipients. The FTIR spectra of the pure drug and formulated granules were recorded using the FTIR-1700 Shimadzu analyzer. The spectra were obtained using the KBr pellet method, and characteristic peaks were analyzed to confirm the presence of functional groups and ensure compatibility between the drugs and excipients [17].

Melting point determination

The melting point of the drug's was determined by Melting point determination apparatus. The drug was filled in a capillary tube and the melting point was measured with the help of a thermometer.

PREPARATION OF GRANULES:

The granules from polyherbal ethanolic extract were prepared through wet granulation method. In this method the two herbal extracts were taken in same ratio and mixed with the excipients. Both drugs Ashwagandha extract and lychee seed extract was mixed with the excipients that are starch, lactose, Crospovidon and magnesium stearate, talc, etc. in the ratios mentioned below in Table 1.

Table 1 Formulation table of Nutraceutical Granules

FORMULATION CHART OF NUTRACEUTICAL GRANULES						
INGREDIENTS	F1	F2	F3	F4	F5	ROLE OF INGREDIENTS
Ashwagandha	3.5gm	3.5 gm	3.5 gm	3.5 gm	5gm	Drug
Lychee Extract	3.5gm	3.5 gm	3.5 gm	3.5 gm	5gm	Drug
Lactose	2.5gm	-	5 gm	10 gm	60 gm	Diluent
Starch	-	2.5 gm	-	3.5 gm	7 gm	Diluent/ Binder
Crospovidon	-	-	1 gm	2 gm	2.5 gm	Disintegrant
Croscarmellose sodium	-	1 gm	-	-	-	Disintegrant
Polyvinyl Pyrrolidone (PVP K-30)	-	1.5 gm	1.5 gm	-	-	Binder
Micro-crystalline Cellulose (MCC)	2 gm	-	-	-	-	Binder
Citric acid anhydrous	0.5 gm	-	-	-	-	Taste Masking agent
Magnesium Stearate	1.5 gm	1.5 gm	1.5 gm	1.5 gm	2 gm	Lubricant
Methyl Paraben	0.2 gm	0.2 gm	0.2 gm	0.2 gm	0.5 gm	Preservative
Propyl Paraben	0.2 gm	0.2 gm	0.2 gm	0.2 gm	0.2 gm	Preservative



FORMULATION OF GRANULES:

First, weigh the accurate amount of both drugs and excipients. The weighed drug and excipients are then taken into a mortar-and-pestle and mixed well. The binder was dissolved in ethanol, which was soluble to API. Then, the binder solution was mixed with the liquid API and poured into the powder mixture while blending to achieve a homogeneous mixture. The addition of the liquid mixture of API and binder to the dry powder forms a dough. The dough was then kept in a hot air oven at about 600 C. After drying for some time, the dough was passed through a sieve and formed into granules. Table 1 lists the composition of granules prepared by wet granulation. After the granules are passed through the sieve no.12 the prepared granules, they were passed through sieve no.88 to separate any remaining powders from the granules, so these unequal granules and powders were removed, leaving granules of the same size on the sieve.

EVALUATION OF POLY HERBAL GRANULES:

Angle of Repose (θ)

Angle of repose was measured by the funnel method to determine the friction forces in granules. Granule formulation was poured through a funnel fixed at 1 cm height (h). The radius (r) of the pile was measured and applied to calculate the angle of repose using the following formula:

$$\theta = \tan^{-1} \left(\frac{h}{r} \right).$$

Moisture content:

The granules were weighed accurately and placed in a desiccator containing Silica gel at 105°C for 24 h. Then the final weight was noted when there was no further change in the weight of granules. The percentage of moisture loss was calculated as difference between initial and final weight with respect to final weight.

$$\% \text{ Moisture content} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Final weight}} \times 100$$

Bulk Density (δ_b)

Bulk density was estimated by pouring the correctly weighed amount (M) of the granule blend into the measuring cylinder. The volume obtained is called bulk volume (V_b) and the density was measured by the given formula:

$$\delta_b = \frac{M}{V_b}.$$

Tapped Density (δ_t)

The bulk mass of the granules was tapped 500 times and the tapped density was calculated by

$$\delta_t = \frac{M}{V_t}.$$

Carr's Compressibility Index

Carr's index shows the compressibility of granules. It was determined by the given formula:

$$\text{Carr's Index} = \left[\left(\frac{\delta_t - \delta_b}{\delta_t} \right) \right] * 100.$$

Hausner's Ratio (H)

Hausner's ratio was calculated by dividing tapped density to bulk density as follows:

$$H = \frac{\delta_t}{\delta_b}.$$

Drug Content:

10 mg of granules were weighed and powdered and 5mg equivalent weight of lychee powder and 5mg equivalent weight of ashwagandha extract was accurately weighed and transferred into a 100 ml volumetric flask. It was dissolved and made up the volume with phosphate buffer pH 7.4. Subsequently the solution in volumetric flask was filtered and suitable dilutions were made and analyzed at 260nm using UV-Visible spectrophotometer. The drug content of each sample was estimated from standard curve of Lychee seed and Ashwagandha using phosphate buffer PH 6.8. **Acceptance Criteria is 90–110%** of the labelled claim. **Importance** Ensures granules contain the correct amount of API [18].

In Vitro drug release Dissolution



Apparatus: USP Apparatus 2 (Paddle type)

Medium: As specified in the monograph (e.g., 900 ml of 0.1N HCl or phosphate buffer)

Temperature: Maintain at $37.0 \pm 0.5^\circ\text{C}$

Paddle Speed: As specified (usually 50 or 75 rpm)

Procedure:

We evaluated the in-vitro dissolution of the granules using a USP apparatus type-II, which is the paddle type. We took granules that were equivalent to 1g of the drug and placed them in 900 ml of a 0.1M HCl buffer, serving as the dissolving medium. This was done at a temperature of $(37 \pm 0.5)^\circ\text{C}$, with the paddle spinning at 100 revolutions per minute. At intervals of 15, 30, 45, and 60 minutes, we collected 5ml samples

from the dissolving medium and promptly replaced them with fresh medium. To measure the drug release at these various time points, we used a UV-visible Spectrophotometer (Elico SL-210) set to 260 nm after proper dilution. We calculated the percentage of drug release and plotted a graph against time. This graphical method allowed us to compare the dissolution patterns, using the concentrations of the reference markers at different time points to evaluate the extent of dissolution [19].

RESULT & DISCUSSION

Phytochemical analysis of Ashwagandha Powder and Lychee seed powder

The phytochemical screening of the extract revealed the presence and absence of various phytoconstituents, as summarized in Table 2.

Table 2 Phytochemical analysis of Ashwagandha and Lychee ethanol extract

Sr No	Phytoconstituents	Ashwagandha ethanol extract	Lychee ethanol extract
1	Alkaloids	+	+
2	Flavonoids	+	+
3	Tannins	-	+
4	Saponins	+	+
5	Terpenoids	+	+
6	Phenols	+	+
7	Glycosides	+	+
8	Cardiac Glycosides	-	-
9	Carbohydrates	+	-
10	Reducing sugar	+	+
11	Protein & amino acids	+	-
12	Resins	+	-

DETERMINATION OF CALIBRATION CURVE

1. Spectroscopy study of the Ashwagandha powder

The Ashwagandha extract solution was taken in distilled water and was taken in a standard cuvette and scanned in the range of 200-800 nm in UV spectrophotometer. It exhibits maximum wavelength at 231 nm as shown Figure 2.

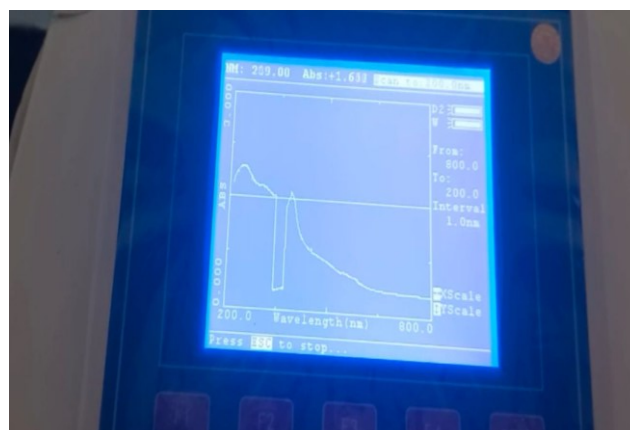


Figure 2 Ashwagandha maximum wavelength



2. Determination of standard calibration curve of Ashwagandha extract:

The UV spectrum of Ashwagandha extract in distilled water (pH=7) showed absorption maxima at 231 nm. The absorption maxima were found to perfectly correspond with those reported in the literature. The

standard calibration curve of Ashwagandha showed linearity with an R² value of 0.9747 at 231 nm wavelength, which is given in Figure 3. The drug content in most in vitro samples obtained during the studies was determined by utilizing the slope of the standard curve. The absorbance of different concentrations is given in Table 3.

Table 3 Absorbance of Ashwagandha extract UV calibration curve

Stock Solution taken (ml)	Distilled water(ml)	Concentration (ppm)	Absorbance
0	10	0	0
0.2	9.8	2	0.146
0.4	9.6	4	0.187
0.6	9.4	6	0.249
0.8	9.2	8	0.322
1	9	10	0.399
1.2	8.8	12	0.434
1.4	8.6	14	0.499
1.6	8.4	16	0.541
1.8	8.2	18	0.571
2	8	20	0.613

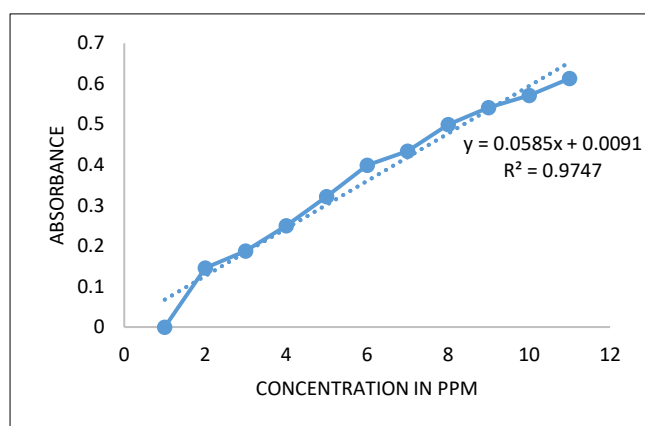


Figure 3 Linearity graph of standard Ashwagandha drug

3. Determination of standard calibration curve of Lychee seed extract:

The UV spectrum of lychee seed extract in distilled water (pH=7) showed absorption maxima at 278 nm. The absorption maxima were found to perfectly correspond with those reported in the literature. The standard calibration curve of lychee seed showed linearity with an R² value of 0.9712 at 278 nm wavelength. The drug content in most in vitro samples obtained during the studies was determined by utilizing the slope of the standard curve. The absorbance of different concentrations is given in Table 4.

Table 4 Absorbance of Lychee seed extract UV calibration curve

Stock Solution taken (ml)	Distilled water(ml)	Concentration (ppm)	Absorbance
0	10	0	0
0.2	9.8	2	0.122
0.4	9.6	4	0.143
0.6	9.4	6	0.182
0.8	9.2	8	0.228
1	9	10	0.266
1.2	8.8	12	0.302
1.4	8.6	14	0.371
1.6	8.4	16	0.379



1.8	8.2	18	0.416
2	8	20	0.438

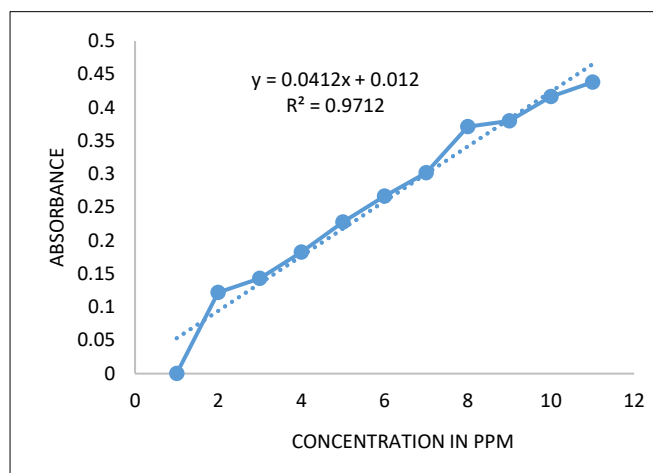


Figure 4 Linearity graph of standard Lychee seed drug

Determination of melting point:

The melting point of Ashwagandha was 190°C, as determined using the melting point determination apparatus.

The melting point of Lychee seed was 128°C, as determined using the melting point determination apparatus.

PHYSICAL EVALUATION OF GRANULES:

Table 8 Physical evaluation of Nutraceutical granules

Physical evaluation	F1	F2	F3	F4	F5
Shape	Irregular	Irregular	Spherical	Irregular	Spherical
Colour	Dark brown	Light brown	Brown	White	Creamy white
Texture	Coarse	Coarse	Coarse	Coarse	Coarse
Odour	Characteristic	Characteristic	Characteristic	Characteristic	Characteristic

EVALUATION OF GRANULES:

Table 9 Evaluation of granules

Granules evaluation parameter	F1	F2	F3	F4	F5
Angle of Repose	29.46 ⁰	30.44 ⁰	28.12 ⁰	24.16 ⁰	25.68⁰
Bulk density	0.75mg/ml	0.63mg/ml	0.49mg/ml	0.75gm/ml	0.43gm/ml
Tapped density	1.25mg/ml	0.95mg/ml	0.57mg/ml	0.88 gm/ml	0.48gm/ml
Carr's index	40%	31.57%	14.03%	14.77%	10.41%
Hausner's ratio	1.49	1.50	1.16	1.17	1.11
Flow Property	Poor	Poor	Good	Good	Excellent

Drug Content (Mg):

Table 10 Result of Drug content

BATCH	DRUG CONTENT
F3	89.1%
F4	92.8%
F5	97.5%

We took a close look at three batches of nutraceutical granules F3, F4, and F5 to see how much active

ingredient they contained. The results were pretty impressive, with F3, F4, and F5 showing 89.1%,



92.8%, and 97.5% of the label claim, respectively. Overall, these numbers suggest that the content is generally acceptable, although F3 is just shy of the lower limit (85%) that's usually needed for single-dose uniformity. On the other hand, F5 really stands out as the top performer, coming closest to the ideal 100% label claim and showcasing the most accurate drug content as given in. According to standard guidelines for content uniformity (like USP <905> and WHO), each individual dose should fall within 85–115% of the average content, with the mean

typically needing to be within $\pm 15\%$, and none should stray outside of $\pm 25\%$.

In-Vitro Drug Release:

To assess the drug release behaviour of formulations F3, F4 and F5 an in-vitro drug release research was carried out during a 30-minute period Table 11 and Figure 8 show the cumulative percentage of medication release from each formulation at various time intervals.

Table 11 Result of In-Vitro Drug Release

TIME (Sec)	IN-VITRO DRUG RELEASE		
	F3	F4	F5
0	0	0	0
20	8.006896552	9.248275862	10.59827586
40	16.47931035	18.69827586	21.63103448
60	25.4637931	28.55172414	33.08275862
80	34.66551724	39.02586207	44.75172414
100	44.02241379	49.77931034	56.74655172
2	53.56551724	60.67241379	69.87413793

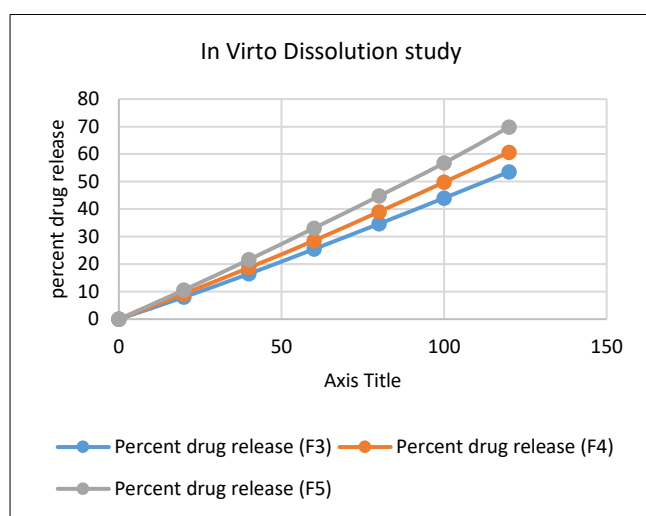


Figure 8 In Vitro Dissolution study

CONCLUSION

From the overall evaluation of granule characteristics, drug content, and in-vitro dissolution performance, F5 has emerged as the most promising batch, having the best flow property, good granule shape and uniformity, highest drug content, and drug release within 2 minutes. Optimized use of the disintegrants and diluents has greatly contributed to the better performance of this formulation. Hence, F5 can be

regarded as the best formulation for fast-dissolving nutraceutical granules, especially in relation to patient compliance and faster onset of action.

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