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RESEARCH ARTICLE

Formulation and Evaluation of Multivitamin Soft Gelatin Capsules: Development, Optimization, and Stability Analysis

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ABSTRACT

This study aimed to develop a soft gelatin capsule dosage form containing multivitamin and mineral suspensions to address dietary deficiencies and meet varying nutritional requirements. Multivitamin and mineral supplements in soft gelatin capsules are popular due to convenience, stability, and improved absorption rates. Objective of the study is to formulate and test a soft gelatin capsule with suspended multivitamins and minerals to guarantee stability, content uniformity, and conformity to official standards. Preformulation studies on active pharmaceutical ingredients (APIs) included visual observation, solubility determination, loss on drying, and sulphated ash. Multivitamin soft gelatin capsules were prepared by encapsulating a stable dispersion of the active drug in a gelatin shell made from glycerin, purified water, and gelatin powder. The fill consisted of soybean oil, hydrogenated vegetable oil, and soy lecithin. After encapsulation, the capsules were inspected for viscosity, bloom strength, weight uniformity, disintegration, and assays. Formulation F5 proved to be stable under accelerated storage conditions, with assay values falling within acceptable limits. The soft gelatin capsules exhibited uniform appearance, fill weight, hardness, and disintegration time. The physical characteristics and content uniformity complied with the official specifications. The stability study showed that the formulation did not undergo any degradation after storage for two months. We developed high-quality multivitamin soft gelatin capsules with good content uniformity, stability, and physical characteristics. The formulation effectively protects against degradation and ensures the stable delivery of multivitamins and minerals. Further bioavailability studies and clinical trials are needed to assess its therapeutic effects.

Keywords: Soft Gelatin Capsules; Multivitamins; Stability Testing

INTRODUCTION

The oral administration of drugs is the most appealing route of administration because of its many advantages. Solid oral tablets are among the most favored options because they are simple to manufacture, easy to consume, offer exact dosing, and are more stable than oral liquids.[1] Capsules are the first dosage form to be selected for orally administered drugs, even though they can be administered through the rectum or vagina. Capsules have been extensively utilized in clinical trials and drug development. From the patient's point of view, capsules provide an odorless and tasteless delivery system, as they do not require a secondary coating process. Capsules are more easily swallowed by several patients than tablets. Active pharmaceutical ingredients (APIs) and excipients required to formulate the API are generally contained in a small hard or soft gelatin shell in the capsule. Following drug delivery, gelatin dissolves in body fluids in the intestine, and the therapeutic compounds within the capsule are released.[2] A soft gel capsule (SGC) is a single, closed soft gelatin vessel that contains a liquid, suspension, or semi-solid material, referred to as the fill. Soft gelatin shells are usually made of film-forming substances such as gelatin and water-soluble or water-dispersible plasticizers, which provide flexibility. Coloring agents, flavorings, sweeteners, drugs, and preservatives are some of the optional additives. Soft gel capsules can also be coated to protect against stomach acids for certain purposes. Soft gelatin capsules are frequently used in the dietary supplement market for the delivery of liquids, suspensions, pastes, and powders.[3] Soft gelatin capsules, a dose form of close to a hundred years, have acquired tremendous importance as a vehicle for medication since the 1930s. This is because numerous unstable drugs,

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which are susceptible to oxidation, light, heat, or humidity, can be safely encapsulated without losing their effectiveness. The production of soft gelatin capsules requires skilled and experienced human resources, proper management, and a well-planned and designed facility in which GMP and environmental conditions for manufacturing are fulfilled.[4]

SGC offers the advantage of delivering therapeutic agents that require very low doses with exactness, for example, cardiac glycosides and vitamin D analogs. They are available in a wide variety of sizes, shapes (including spherical, elliptical, and oblong shapes as well as custom tube shapes with and without twist-off), and colors, leading to many attractive finished products for consumers. For oral use in humans, SGC must not be larger than 20 mm oblong, 16 mm oval, and 9 mm round.[5] SGCs were manufactured under conditions controlled by a precise temperature and humidity. The process consisted of the following steps: gelatin paste preparation, preparation of the fill material (API or nutrients), encapsulation, drying and examination of the capsules, and storage and packaging.[6–8] In the US, multivitamins/mineral supplements fall under dietary supplements with a minimum of three vitamins and minerals but no herbs, hormones, or drugs, and follow the Food and Drug Administration standards for safe doses to avoid unhealthy results. Multivitamins usually consist of lipid-soluble vitamins such as vitamins A, D, E, and K., and water-soluble vitamins such as thiamine (vitamin B1), riboflavin (vitamin B2), vitamin B6, vitamin B12, vitamin C, folic acid, niacin, pantothenic acid, and inositol. They also include minerals, such as calcium, Phosphorus, Iron, Iodine, magnesium, manganese, copper, and zinc.

Gelatin capsules are also widely employed as carriers of specific vitamins, minerals, and pharmaceuticals. Gelatin is widely utilized in the food industry, especially in vitamin and mineral capsules, due to its digestibility and compatibility with many vitamins, minerals, and APIs.[9] The Recommended Dietary Allowance (RDA) or Adequate Intake (AI) is the norm of a balanced diet, establishing the minimum quantities of necessary vitamins and nutrients to meet the population's health needs.[10,11] Some of the multivitamin soft gelatin capsules available in the market are Revital capsules (Vitamin B1, B2, B6, B5, C, E and minerals like Ca+, Fe, Mg, Mn, Zn, Cu and Ginseng), Moringa capsules (Vitamin- B1, B2, B6, B3, B7, Vitamin -C, A, D, E, K.), Nergipot capsules (Vitamin and mineral supplement), Riva-L capsule (Lysine, B1, B2, B6 and B12, and simavite capsule (Vital minerals and vitamins). The main objective of this study was to develop a soft gelatin capsule dosage form of a suspension of multivitamins and minerals. The formulation seeks to fulfil the nutritional levels required for dietary supplements to correct vitamin deficiency.

MATERIALS AND METHODS

Pre-formulation and Drug Characterization

The general appearance of all pure active pharmaceutical ingredients (APIs) was examined by visual observation of color, surface homogeneity, shape, and appearance. Solubility tests for water-soluble and oil-soluble vitamins were qualitatively performed using various solvents. Loss upon drying was measured by comparing the weight of the sample before and after drying under the specified conditions. The sulphated ash test was carried out in a silica crucible by heating and weighing to a constant weight. API samples were visually examined for foreign matter.

Formulation Development of Multivitamin Soft Gelatin Capsules

Soft gelatin capsules of multivitamin were prepared by coating a suspension of multivitamin inside a soft gelatin shell. Its preparation includes two important steps: preparing the fill medicament and capsule shell material.

Preparation of Fill Medicament

Magnesium sulphate heptahydrate was dried in a tray dryer for five hours to eliminate the excess moisture. The soybean oil was filtered through a #100 mesh and transferred to a stainless-steel vessel to maintain purity. Hydrogenated vegetable oil and soya lecithin were heated and blended thoroughly before the addition of ethyl vanillin. Different vitamins and minerals were reduced in size using a cad mill and then mixed with filtered soybean oil. The suspension was then homogenized and de-aerated under vacuum to remove air bubbles and to obtain a stable and uniform mixture. Finally, the developed filler material was tuned by assessing the impacts of varying levels of soybean oil, soya lecithin, and hydrogenated vegetable oil on viscosity, suspendability, and stability to ensure that the final product conforms to quality requirements.

Preparation of Gelatin Shell

Gelatin shells were prepared by heating a mixture of glycerin, purified water, and gelatin powder. The mixture was heated to avoid lumps and air bubbles, and vacuum was drawn out to further de-aerate the mixture. The colorant (Ferric Oxide Black) was dispersed and thoroughly mixed into the gelatin paste. Gelatin paste was maintained under controlled temperature conditions until use. The gelatin shell composition was optimized using different concentrations of glycerin, sorbitol, and PEG 400 to analyze their effect on leakage, formation of soft gel, sealing, and drying.

Encapsulation Process

Encapsulation was performed using a rotary encapsulation machine. The die roll was modified with reference to the fill volume, dependent on viscosity, solid content, particle size, and suspending agent concentration. The encapsulation machine was equipped with standard change parts and the fill weight was manipulated using soybean oil. Tumble drying of the filled capsules for 30 min preceded their transfer to the tunnel drier.

Drying Process

The encapsulated soft gelatin capsules were dried in a tunnel drier at 28 ± 2°C. The tumble drier first removed the bulk moisture and then further dried under controlled conditions for a maximum period of 24 hours.

Post-Encapsulation Processes

The capsules were initially cleaned with a wiping pan for 30–45 min to eliminate excess gelatin or surface film. They were then run using a sizing machine to remove size differences and achieve uniformity. A visual check was then performed to identify any malformed or misfilled capsules, leaving only high-quality capsules for further processing. Once final quality acceptance was obtained, the capsules were filled into blister packs and HDPE containers. Stability testing was also performed under various temperature and humidity conditions according to ICH guidelines to determine the long-term stability and integrity of the capsules. This approach guarantees the effective development and optimization of multivitamin soft gelatin capsules with the desired quality characteristics.

Evaluation of Soft Gelatin Capsules

Evaluation of Gelatin Shell Parameters:

- **Viscosity Determination:** Viscosity of the gel mass was found to be an important factor in the smooth production of soft gelatin capsules. Approximately 200 g of the prepared gel mass was maintained at 55–60°C and the viscosity was measured using a Rheometric Scientific Viscometer. Spindle number 2 was employed at a shear rate of 20 rpm for 45 seconds, and the viscosity was noted on the mps-scale. Triplicate readings were taken to ensure precision.
- **Bloom Strength of Gelatin :** The bloom strength was measured to determine the mechanical strength of the gelatin shell. Gelatin (7.50 g) was carefully weighed and dissolved in 105 g distilled water at 61°C. The solution was then cooled in a 10°C water bath for 16–18 hours. The gel sample was then positioned on the platform of a texture analyzer, in which a plunger was utilized to measure the mechanical strength.
- **Determination of Loss on Drying (LOD):** The moisture content of the gelatin shell was measured using the loss on drying method. An empty glass-stopper bottle was weighed, and the allocated sample was inserted inside it. The sample was dried for 30 min at 60°C, and its weight was recorded after cooling in a desiccator. The percentage LOD was calculated with respect to the weight difference, and soft gelatin shells usually contain 6–13% water.

Evaluation of Optimized Soft Gelatin Capsules

- **Description:** The overall appearance of the capsules was visually inspected for color, shape, external film quality, and uniformity.
- **Average Weight:** The weight of 20 capsules chosen at random was measured, and the average weight was determined using the formula outlined in the U.S. Pharmacopeia.
- **Average Fill Weight:** Fill weight was determined by measuring 20 capsules and deducting the weight of 20 empty shells. Weight uniformity was calculated as the percentage deviation between the low and high fill weights.
- **Hardness Test:** The hardness of the capsules was determined by using a Barreiss Hardness Tester. Ten capsules were chosen, and the amount of force required to compress each capsule to 3 mm was measured in Newtons. The average hardness was determined from five randomly chosen capsules.[12]
- **Disintegration Test:** The Disintegration time was tested using a Disintegration Test Apparatus. Six capsules were placed in the assembly, and discs were placed in each tube. The bath temperature was set to 37±2°C, and the time taken for full disintegration minus shell fragments was measured.

Assay by HPLC

- **Assay for Water-Soluble Vitamins:** The contents of vitamins B1, B2, B3, B5, B6, B9, B12, vitamin C, and choline bitartrate were analyzed by High-Performance Liquid Chromatography (HPLC). The assay was carried out on an Inertsil ODS-3 column with a mobile phase of potassium dihydrogen orthophosphate and methanol. A gradient program was provided for the effective separation of the components. Standard and sample solutions were obtained by dissolving vitamins in water or appropriate solvents and examined under controlled chromatographic conditions.
- **Assay for Minerals:** Mineral content, such as copper, zinc, manganese, potassium, magnesium, and iron, was determined by Inductively Coupled Plasma Spectroscopy (ICAP). Sample solutions were obtained by digesting the capsule in concentrated nitric acid and diluting it with water. Standard calibration solutions

were prepared for quantitative determination.

Determination of Related Substances by HPLC

The related substances were analyzed using HPLC with an Inertsil ODS-3 column and a mobile phase of potassium dihydrogen orthophosphate and methanol. The gradient program was optimized to separate impurities. Sample solutions were prepared by dissolving the capsule fill in suitable solvents, and its compositions were determined based on standard solutions.

A stability study was performed for the prepared soft gel capsules to evaluate the quality of the drug product, which varies with time under the influence of various environmental factors such as temperature, humidity, and light (some of the vitamins are light-sensitive). Recommended storage conditions, re-test periods, and shelf life.[13] The Joel Davis stability test was performed for SGCs by packing the formulation in sealed containers with a silica gel lining, which protects against moisture absorption from the surroundings.[14] These containers were then stored at 400°C and 75% relative humidity for two months and assessed based on physical appearance, loss of drying, and other parameters.

This systematic testing guaranteed that the soft gelatin capsules fulfilled the desired pharmaceutical quality standards based on their physical, chemical, and mechanical properties.

RESULTS

Before formulation, pre-formulation studies on Active Pharmaceutical Ingredients (APIs) were carried out. Different formulation parameters were tested to determine product stability and efficacy. Five different fill medicament compositions (F1, F2, F3, F4, and F5) were developed during the formulation development phase of the multivitamin soft gelatin capsules. Formulations F1, F2, F3, and F4, with multivitamins, minerals, and hydrogenated vegetable oil, failed to form a stable suspension because the level of soya lecithin was too low, resulting in weak viscosity and consistency. Composition F5, with multivitamins, minerals, soybean oil, and soya lecithin, was spontaneously dispersible and had satisfactory consistency and viscosity, rendering it the best suspension fill.

The composition of gelatin shell was made from the gel pastes, which were subsequently employed in encapsulation (Table 1). In testing the soft gelatin capsules, the gelatin solution's viscosity was within the acceptable range of 20-40 mps, reflecting proper flow and lack of flow during encapsulation. The bloom strength of gelatin was also tested and was found to be within the normal range of 150-250. The drying loss of the capsule shell, which is usually 6% to 13% water, was also within the acceptable range.

Table 1: Gelatin shell compositions

Sl no.	Ingredients	P1	P2	P3	P4
1	Gelatin-B	45%	45%	45%	45%
2	Glycerin	_	_	10%	20%
3	Sorbitol	20%	10%	10%	_
4	PEG 400	_	10%	_	_
5	Titanium dioxide	0.25%	0.25%	0.25%	0.25%
6	Ferric oxide black	0.08%	0.08%	0.08%	0.08%
7	Purified water	34.65%	34.65%	34.65%	34.64%
	Results	Leakage of capsules and decreased hardness (<2N)	Paste was thin and sealing was not achieved	Soft capsules were obtained and took a long time for drying	All factors achieved and hardness achieved (5-8N)

For the optimized formulation, soft gelatin capsules were tested for general appearance, weight, and other physical attributes. The capsules were found to be oblong, black, and pleasing in appearance (Figure 1). The capsule weight variation averaged from 12.40% to 13.10% in F5, which is within the acceptable limit of ±2.0%. The uniformity of the fill weight was between -0.57% and +1.12%, which was again within the official limits of ±2%. The capsule hardness varied from 6.4N to 7.5N, which falls in the normal range of 5-8 Newtons. The disintegration time of the capsules was found to be below 12 min, which is optimum because official limits are not provided for soft gelatin capsules. In addition, the related substances present in F5 were within an acceptable impurity level of 0.50%.

Fig. 1: Appearance of soft gel capsules

Accelerated stability testing of F5 was conducted for two months at 40 ± 2°C and 75% RH ± 5%. The test results

showed the satisfactory stability of the in-house product. The F5 assay was 110% at 1 month and 106.92% at 2 months, both within acceptable limits. The levels of related substances in F5 were within the range of 0.50% at both 1-month and 2-month stability tests.

DISCUSSION

The primary aim of the present study was to formulate a generic multivitamin supplement in suspension to fulfil the requirements of consumers who suffer from nutritional deficiencies or have diverse nutritional needs. The present market has widely accepted multivitamin and mineral supplements because of its convenience, high stability, and absorption values. Stephen et al.[15] carried out a study on Diclofenac potassium liquid-filled soft gelatin capsules (DPSGC), with the objective of assessing the efficacy and safety of DPSGC 25 mg in a large-scale, double-blind, placebo-controlled trial in patients with pain. The results indicated that DPSGC effectively relieved pain in patients, suggesting that this new formulation of diclofenac potassium may be an effective treatment for mild to moderate acute pain. Gennadios et al.[16] filed a patent for a soft gelatin composition in the form of 30-60% weight film-forming material, 5-35% weight water-dispersible material, and 25-65% weight purified water. The film-forming material consisted of gelatin and gum acacia. Gelatin-extended capsules had physical properties similar to those of control capsules but revealed greater elasticity when the gelatin-gum acacia mixture was formed and showed superior stability.

The major challenge encountered in the formulation of SGCs of multivitamins and minerals is the development of consistently stable suspension fills. This was mainly because the formulation contained both fat- and water-soluble vitamins and minerals. The pre-formulation investigation of the active ingredients was within the IH limits. The physicochemical parameters of the soft gelatin capsules were in accordance with the official standards. The capsules were satisfactory with no color change, blooming, or leakage. The in vitro test parameters of the capsules complied with official standards. The results of multivitamin and mineral assays were within the normal range. The F5 formulation had good stability after two months at 40°C and 75% RH. Soft gelatin capsules provided protection against degradation, and this is an effective formulation method. The advantages of soft gelatin capsules extend beyond multivitamins, as seen in studies on other formulations such as diclofenac potassium SGCs, which also demonstrated effective delivery and stability.[3,17] However, challenges remain in optimizing shelf-life and stability of various formulations, necessitating ongoing research in this area.[3]

CONCLUSION

In summary, this study successfully developed a soft gelatin capsule dosage form of multivitamins in suspension form as an effective dietary supplement to address nutritional imbalance and vitamin deficiencies. The pre-formulation studies and physicochemical parameters of the capsules were within acceptable limits without any defects such as color change, blooming, or leakage. The capsules showed satisfactory stability under accelerated conditions, and the optimized formulation exhibited content uniformity and protection against degradation. This process is an effective method for formulating multivitamin soft gelatin capsules, and further research on bioavailability and clinical trials are suggested to evaluate their therapeutic potential.

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