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RESEARCH ARTICLE

VEGETARIAN CAPSULES: A LOGICO-ETHICAL SUBSTITUTE.

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Abstract

Capsules have been the most preferred and effective mode of oral dosage. Conventionally, capsules were made from gelatin which had its source from domesticated cattle, chicken, pigs, horses and fish. Gelatin based capsules have several disadvantages ranging from allergy, hygroscopicity and limited usage for liquid and gel-based drugs. Vegetarian Capsules provide a wide range of opportunities to overcome the shortcomings of Gelatin based capsules. Also, Vegetarian capsules in addition to being both the obvious choice for both vegetarian and vegan consumers are also more acceptable for religious reasons. Vegetarian capsules are often deemed suitable to be classified as both Kosher and Halal products, and also for other religions following either vegetarianism or restrictions on particular animal consumption. This review paper studies the various plant-based raw materials that are used for manufacturing Vegetarian Capsules. Also, various blends used for improved properties in these capsules are investigated. The properties, advantages and disadvantages of the Vegetarian Capsules, along with the applications of these capsules in various medicinal dosages are discussed.

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Introduction:-

Oral dosage is most effective and widely used form of medication. Oral dosage mainly includes tablets, capsules and syrup. Capsules are defined as solid dosage forms in which the medication is enclosed within shells. The medication can be of liquid, solid or semisolid type and can be administered orally, rectally or vaginally. The word 'capsule' is derived from the latin word 'capsa', meaning 'chest, box, case'.

The capsules shells used today for drug administration are mainly made of Gelatin. Gelatin is produced by partial hydrolysis of collagen extracted from the skin, bones, and connective tissues of animals such as domesticated cattle, chicken, pigs, horses and fish. Thus, the consumption of Gelatin is a problem for the followers of various religions (Islam – Halal, Judaism – Kosher, Jainism, Hinduism, etc.). Also, gelatin based capsules have certain disadvantages, like limited compatibility with some liquids and gels, gelatin allergy for some individuals, potential toxicity, highly hygroscopic nature resulting in storage difficulty and limitations in hygroscopic preparations, etc. Thus, vegetarian cellulose based capsules are the best alternative to the gelatin based capsules. Vegetarian capsules in addition to being both the obvious choice for both vegetarian and vegan consumers are also more acceptable for religious reasons. Vegetarian capsules are often deemed suitable to be classified as both Kosher and Halal products and are acceptable for Hindus and Jains as well. The scientific advantages of vegetarian capsules are their availability in various colours and sizes, good compatibility with drugs having liquid, semisolid and gel composition, no potential health risks and no toxicity. [1-2] The first vegetable capsule which is made of HPMC were produced in 1989 by G S Technologies Inc. with trade name "Vegicaps".

In recent years, extensive research has been done on commercializing vegetarian capsule shells, resulting into success.

Gelatin capsule shells:-**Advantages:-**

1. Provides a tasteless, odorless means of administering medication.
2. The ready solubility of gelatin at gastric pH provides rapid release of medication in the stomach.
3. Since hard gelatin capsules may be compounded by the pharmacist, this dosage form offers physicians greater flexibility in dosages and drug combinations than is available with prefabricated medication.
4. Neat and elegant in appearance, can be transparent as well as colored to protect the drugs from light.

Disadvantages:-

1. Cross linking of gelatin on contact with aldehydes and subsequent drug incompatibility.
2. Transparent low-color capsules are difficult to produce owing to the effect of the intrinsic Maillard reaction on gelatin color.
3. Origin of the gelatin capsules is a major disadvantage for individuals with religious or dietary restrictions.
4. Gelatin capsules are only suitable for use with powdered medications or supplements. Liquids and various other materials such as gels are not compatible with capsules made of gelatin.
5. Can cause irritation to individuals allergic to bovine products.[3]

Need for vegetarian capsule shells:-

One of the most obvious advantages of using cellulose based or vegetarian capsules is that they are not made with animal byproducts. This distinct characteristic allows them to be suitable for individuals who choose not to consume products sourced from animals. Vegetarian capsules in addition to being both the obvious choice for both vegetarian and vegan consumers are also more acceptable for religious reasons as well. In fact, vegetarian capsules are often deemed suitable to be classified as both Kosher and Halal products. This opens the option for a larger customer base. These capsules are available in various colors and sizes, and are more flexible in their application. Cellulose is the preferred capsule base for substances that have more of a semi solid or gel composition. They are also an ideal choice for oxidation-sensitive ingredients such as essential oils. Additionally, vegetarian capsules have no known potential health risks, even when consumed in a long term scenario as they are 100% natural and nontoxic.[4-5]

Vegetarian Capsule Shells	Tablets
Without Preservatives.	Preservatives are to be added.
Ideal for hygroscopic preparations.	Not ideal.
Fast dissolving ensuring better bioavailability.	Delay in dissolving.
Free from irritants, inactive binders, colours.	They are to be added.
Hides the taste and odour of the medicine.	Does not.

Raw Materials and Ingredients of Vegetarian Capsules:-**HPMC (Hydroxypropylmethylcellulose):-**

Vegetable capsule shells are mostly prepared from the hydroxypropyl methylcellulose (HPMC), most commonly known as hypromellose. It is produced by synthetic modification of the naturally occurring polymer cellulose and is considered safe for normal consumption in human- (1) as a coating polymer, (2) as a bioadhesive, (3) thickening agent in controlled release systems, (4) in solid dispersion to enhance drug solubility (5) and as a binder. The material is described as a white to slightly off-white powder or granules, practically insoluble in hot water, in acetone, in dehydrated ethanol and in chloroform, but dissolves in cold water giving a colloidal solution owing to the reversible thermal gelation property. HPMC is available in different type of groups with limits on methoxy and hydroxypropoxy groups. These groups affect many of the HPMC properties such as gelation temperature, viscosity, flexibility and hydration.

Hypromellose in an aqueous solution, unlike methylcellulose, exhibits a thermal gelation property. That is, when the solution heats up to a critical temperature, the solution congeals into a non-flowable but semi-flexible mass. Typically, this critical (congealing) temperature is inversely related to both the solution concentration of HPMC and the concentration of the methoxy group within the HPMC molecule (which in turn depends on both the degree of substitution of the methoxy group and the molar substitution. That is, the higher the concentration of the methoxy group, the lower the critical temperature. The inflexibility/viscosity of the resulting mass, however, is directly related to the concentration of the methoxy group (the higher the concentration, the more viscous or less flexible the

resulting mass is). This gelation property of HPMC is the main reason why it is suitable for the preparation of capsules.

Synthesis techniques for HPMC:-

General Procedure for Alkali Cellulose Ethers:-

In general, cellulose ethers are manufactured by reaction of purified cellulose with alkylating reagents under heterogeneous conditions, usually in the presence of a base, typically sodium hydroxide, and an inert diluent. Cottonseed linter fiber and wood fiber are the principal sources for cellulose. Purified cellulose cotton linters, commonly termed chemical cottons, are generally of higher purity and higher maximum molecular weight than purified cellulose from dissolving grades of wood pulp. The base, in combination with water, activates the cellulose matrix by disrupting hydrogen-bonded crystalline domains, thereby increasing accessibility to the alkylating reagent. This activated matrix is commonly termed alkali cellulose. Other reagents may be used in combination with sodium hydroxide, such as ammonia, surfactants, phase transfer agents, or enzymes, to promote formation of a more uniformly activated cellulose matrix.

The base also promotes the etherification reaction. The several purposes of the inert diluent are to suspend/ disperse the cellulose, provide heat transfer, moderate reaction kinetics, and facilitate recovery of the product. The diluent may also help to distribute reagents among fibers to promote a uniform reaction. Crude grades of cellulose ethers, most notably sodium carboxymethylcellulose, may be made in the absence of any diluent. Reactions are typically conducted at elevated temperature, ~50–140°C, and under nitrogen to inhibit oxidative molecular weight degradation of the polymer if so desired.

The alkali cellulose is then reacted with a mixture of propylene oxide and methyl chloride to produce the desired cellulose ether products which are recovered by washing with hot water and drying. When the alkali cellulose is prepared employing sodium hydroxide, the ratio of caustic to cellulose should be maintained at a relatively low value of from about 0.25 to about 0.45, preferably 0.35 to 0.4, part by weight of sodium hydroxide per part of cellulose. If other alkalies are employed, they are used in amounts which are molar equivalents of the amounts specified for sodium hydroxide.

The resulting alkali cellulose is reacted with a mixture containing from about 1.5 to about 4 parts of propylene oxide and from 0.4 to about 0.8 part of methyl chloride per part by weight of cellulose, provided, however, that such weights are adjusted to provide at least 2 moles of propylene oxide per mole of methyl chloride in the reaction mixture. In large scale operation, it is preferred to employ the least proportion of propylene oxide required to obtain the desired.[6]

Method of Synthesis of HPMC:-

20 pounds of ground cotton linters were added to an internally agitated vessel designed for operation under vacuum or pressure. Air was evacuated from the vessel and 14 pounds of aqueous 50 percent sodium hydroxide solution was sprayed onto and thoroughly mixed with the linters.

Thereafter, 80 pounds of propylene oxide and 16 pounds of methyl chloride were added to the vessel with vigorous agitation and the reaction mixture heated gradually over a period of ninety minutes from ambient conditions to a temperature of 60°C, and maintained at 60°C, under autogenous pressure for a further period of about 5.5 hours to complete the reaction. Heating was then discontinued and the vessel was vented and the product recovered by washing with hot water and drying.

The resulting white solid product was soluble in anhydrous methanol and in water, having a gel point of about 43°C, in the latter, and was found by analysis to contain 7.0 percent by weight of methoxyl substitution and 45.0 percent by weight of hydroxypropoxyl substitution, corresponding to a methoxyl degree of substitution of 0.58 and a hydroxypropyl molar substitution of 1.58, respectively.

1 gram of this hydroxypropyl methylcellulose product dissolved readily in 100 grams of anhydrous methanol to produce a clear, viscous solution having a viscosity of 700 centipoises as determined with an Ubbelohde viscometer at 20°C. The methanolic solution was suitable for casting thin water-soluble films and for applying transparent, water-soluble film coatings to tableted pharmaceutical compositions.

In the preferred method of preparing hydroxypropyl methylcellulose ethers, the proportion of methyl chloride is adjusted to provide at least one mole of methyl chloride in the overall reaction for each mole of alkali metal hydroxide incorporated in the alkali cellulose.[7]

Starch:-

Moisture content in starch capsule lies between 12% to 14% w/w, with more than 50% being tightly bound to starch. The presence of this bound moisture indicates that starch capsules may provide better stability properties and reduces susceptibilities to change on storage. Dissolution is similar to that of gelatin capsules.

Capsules are ready for filling immediately following manufacturing. They offer greater resistance to humidity and heat than gelatin and allow easy filling as they are non-static. Dissolution is independent of pH. It has good surface finish. Coating of hard gelatin capsule with aqueous spray formulations can lead to softening of gelatin shell or gelatin shell may become brittle due to water evaporation and drying especially at the onset of coating. On the contrary, the coating of starch capsules seems to be less problematic because of smooth seal of the filled unit, together with the higher bulk density of the capsules, which provide a more uniform coating bed.[8]

Colorants:-

The color of a pharmaceutical product plays an important role in their use. Colour is used principally to identify a product in all stages of its manufacture and use. In the manufacturing company it assists in complying with GMP norms by helping the operators differentiate between products. The colorants that can be used in capsules are of two types: water soluble dyes or insoluble pigments. To make a range of colours dyes and pigments are mixed together as solutions or suspensions. Three most commonly used dyes are erythrosine, indigo carmine and quinolone yellow. The two types of pigments used are iron oxides- black, red and yellow and titanium dioxide which are white and used to make the capsule opaque. Capsules are coloured by the addition of colorants to the solution during the manufacturing stage.

Manufacturing and processing of vegetarian capsules:-**Soft Capsules:-**

Soft capsules consist of one-piece hermetically-sealed soft shells. Soft capsules are prepared by adding a plasticizer, such as glycerin or polyhydric alcohol (e.g., sorbitol), to starch. The plasticizer makes it elastic. Soft capsules come in various shapes such as spherical, elliptical, oblong, and special tube shapes with and without twist off. They can contain non-aqueous liquids, suspensions, pasty materials, or dry powders. They are especially important to contain volatile drug substances or drug materials susceptible to deterioration in the presence of air.

Manufacturing of soft capsules:-

There are several procedures to prepare soft capsules, such as the plate process, the rotary die process, and reciprocating die process. Most soft capsules produced in industry are prepared by the rotary-die process. The film forming hydrocolloid mixture is incorporated in the plasticizer solution (Glycerin, Sorbitol syrup) under continuous mixing and heated upto 80°C. the gel mass is then cooled and grinded into granules. Gel granules are remelted and extruded as ribbons and fed into encapsulating machine. Further, two continuous starch ribbons are brought together between twin rotating dies. At the moment that the dies form pockets of the ribbons, metered-fill material is injected between the ribbons. Then the pockets are sealed by pressure and heat. The capsules are subsequently severed from the ribbon. As the capsules are cut from the ribbons, they may be collected in a refrigerated tank to prevent capsules from adhering to one another and from getting dull.[9-10]

Hard Capsules:-

Hard Capsule are two part encapsulation. They are used for solid or pelletized dosage. The drugs can be taken either by opening two part capsule and spreading the drug on Soft food or directly consumed. In the stomach, warm gastric fluid will dissolve the capsules and drug can circulate. The general polymers that are used for Hard Capsules are HPMC. They have processing similar to that of gelatin based capsule. Hard capsules are generally manufactured by using a dip molding process. In this process, pin molds are dipped into a film forming composition. By gelling the film forming polymer on the pin, a film is formed that is subsequently dried on the pin, to obtain a capsule shells. The shells are then stripped of the pins and cut to a desired length. Thus, capsules caps and bodies are obtained that can later be filled with a substance and joined such that a filled capsule is obtained.

HPMC hard capsules are prepared by first forming an aqueous solution of HPMC in water. The aqueous solution is maintained at temperature of nearly 70°C. The gelling temperature for concentration of 19 % will be around 30-40°C. The aqueous solution is generally used as dipping media.

Starch Capsules are also used as a substitute for gelatin based capsules. Starch capsules are manufactured using "Injection Molding". In case of starch capsules, sealing and filling of substances is done directly. This leads to a finished product which well sealed and resistant to manipulation. Starch capsules have better coloring abilities than Gelatin based capsules. [11]

Blends:-

HPMC/HPS blends had been made with 70% HPS. Polyethylene glycol (PEG) was used as plasticizer. HPMC requires high processing conditions and cost. Also, gelling and drying is carried out at high temperature. Hydropropyl starch has relatively low cost. On addition of HPS, transparency is decreased. Both HPS as well as HPMC are hydrophilic in nature. On addition of HPS, the moisture content in capsules increases and this helps in digestion of capsules.

The solubility of HPMC capsules needs to be increased so that drugs can give maximum clinical performance. Copolymer of PVA can also be used as capsule. The method used is Copolymerizing acrylic acid (AA) and methyl methacrylate (MMA) on PVA as a skeleton and then using the obtained PVA copolymer as capsule shells. The capsules opened in less than 10 min in all the media. PVA copolymer capsules became brittle when water content was less than 4%, but were less brittle compared with gelatin capsules. [12]

Market Report:-

The global empty capsules market was valued at \$1,300 million in 2014. This market is expected to grow at a moderate CAGR during the forecast period of 2014 to 2019 and is estimated to be worth \$1,820 million by 2019. The market is mainly driven by the rising demand for hard gelatin and vegetarian capsules in the pharmaceutical and nutraceutical industries, backed by the increasing number of therapeutic applications. The trend of greater uptake of manufacturing and contract manufacturing services in the pharmaceutical industry is also expected to propel the growth of the empty capsules market during the forecast period. Technological advancements, such as vegetarian capsules or nongelatin capsules, capsule dosing for dry powder inhalers, capsule-in-capsule for sustained release effect, and solid lipid pellet capsules are also expected to contribute to the growth of the empty capsules market in the pharmaceutical and nutraceutical industries.

Capsugel (U.S.) and ACG Worldwide (India) are the leading players of the global empty capsules market, together accounting for around 40% to 50% of the market in 2013. Capsugel has a diversified product portfolio, which includes a wide range of capsules such as hard gelatin and nongelatin-based capsules. [13]

Conclusion:-

Vegetarian Capsules present themselves as great substitute to the conventional Gelatin Capsules. They show properties like hydrophilicity that are better than gelatin capsules. Also, they are safe as compared to Gelatin Capsules. HPMC provides excellent reproducibility with no shortage of raw material as no animal origin products required. Vegetarian Capsule is an emerging market although initial capital investment will be more, products obtained will serve better yields. [14]

Vegetarian Capsule shells	Gelatin Capsule shells
100% vegetarian	Animal derived - cows, bovine product.
HPMC or Hydroxypropylmethyl cellulose is mainly used.	Gelatin is used.
Kosher and Halal certified.	May or may not be Kosher and Halal certified.
Suitable for cultural, religious and vegetarian dietary requirements.	Not suitable for all such requirements.
Stability over wide range of temperature and humidity.	Limited stability.
Perfect for hygroscopic preparations.	Not suitable.
Compatible with capsule filling machines, all sizes available.	Same compatibility.
Doesn't support bacterial growth	Under good storing conditions, it doesn't support bacterial growth.

Reference:-

1. Hydroxypropyl methyl cellulose hard capsules and process of manufacture.- **EP 2078042 A1**
2. <http://www.ijpcsonline.com/files/47-189.pdf>
3. <http://www.capsuledepot.com/differences-between-vegetarian-and-gelatin-capsules/#sthash.p7gJ7gJH.dpuf>
4. https://www.youngliving.com/en_US/products/clear-vegetable-capsules
5. <http://www.capsuledepot.com/differences-between-vegetarian-and-gelatin-capsules/#sthash.p7gJ7gJH.dpuf>
6. United States Patent Office, Patent 3,712,886; Patented Jan 23, 1973- Method for Preparing Cellulose Ether Derivatives
7. United States Patent Office, Patent 3,839,319; Patented Oct 1, 1974- Hydroxypropyl methylcellulose Ethers and method of preparation, Assignee- Greminger, Jr. et al., The Dow Chemical Company, Midland, Mich..
8. Starch capsules: an alternative system for oral drug delivery-Vinod D. Vilivalam, Lisbeth Illum and Khurshid Iqbal, PSTT Vol. 3, No. 2 February 2000
9. Pharmaceutical Capsules by By Fridrun Podczeck, Brian E. Jones
10. Encyclopedia of Polymer Science and Technology, John Wiley & Sons, Inc. Volume 5- Cellulose Ethers, Subtopic- Methyl cellulose and its derivatives
11. Moawia M. Al-Tabakha: HPMC Capsules: Current Status and Future Prospects. J Pharm Pharmaceut Sci. 2010;13(3):428 – 442.
12. Developing hydroxypropyl methylcellulose/hydroxypropyl starch blends for use as capsule materials-Liang Zhang Yanfei Wang Hongsheng Liu Long Yu Xingxun Liu Ling Chen Nouzi Zhang
13. Excerpts from report by Markets and Markets on www.reportbuyer.com
14. Vegetable Capsule Shell-Sheladiya Dipak V, Sodha Hiten, Ketan Shah and Tusharbindu Desai International Journal of Pharmaceutical and Chemical sciences Vol. 1 (3) Jul-Sep 2012