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ORIGINAL ARTICLE

PARTICLE CHARACTERIZATION OF PRE-COMPRESSED GRANULES FOR TABLET FABRICATION USING A NOVEL PHARMACEUTICAL EXCIPIENT

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Abstract:

One of the most efficient processes for producing unit dose medication is the compaction of pharmaceutical powder mixtures into tablets. The acceptability of tablets formulations in the marketplace will be primarily determined by patient acceptance in a class of equal therapeutic value. Therefore appropriate selection and use of components that impact on these properties are of extreme importance. However, the pharmaceutical excipients are required to comply with pharmacotechnical aptness and regulatory qualifications desired and implemented for the purpose. Any potential formulation must have to be financial viable simultaneously for business competiveness. In this connection, granules fabricated with processed watermelon flesh as novel multifunctional pharmaceutical excipient for tablet compression have been evaluated for the pharmaceutical and micromeritic properties towards their potential use in manufacturing of compressed tablets with identified trade merits. Evaluation of granules was performed using drug content particle size analysis, angle of repose, bulk and tapped density measurement, compressibility index, hausner's ratio and water treatment. The particle size distribution was a normal distribution in all the batches. The angle of repose of all batches depicts excellent flow of powder with added glidant which was further supported by compressibility Index and Hausner's ratio. The results prove the potential of formulated granules for successful compression.

KEYWORDS-

Granule characterization, pharmaceutical excipients, drug delivery, pharmaceutical tablets.

INTRODUCTION

Drug delivery systems play an important role in therapeutic performance of medicaments and their commercial success, further these affect the improvement of medication compliance too. The easy administration for the patient and the simple handling of the active drug dose makes the tablet a very favored dosage form worldwide. In view to obtain desired properties of compacts, the usage of powder formulations commonly consisting of one or more additives and it's quite seldom that any therapeutic active medicament given as such in its pure chemical form. In fact the amount of excipients is many times more that the quantity of drug itself. The Pharmaceutical excipients, therefore, have key role to play in formulation of drug delivery systems. They can affect the overall efficiency and cost effectiveness of the dosage form[1]. Formulators apply practical understanding of pharmaceutical excipients to develop optimal, robust formulations and the appropriate manufacturing processes. As with drug substances, excipients are derived from natural sources or are synthesized either chemically or by other means. The International Pharmaceutical Excipients Council defines an excipient as any substance other than the active drug or

prodrug that is included in the manufacturing process or is contained in a finished pharmaceutical dosage form. During the past few years, industry has come to understand better, the excipient functionality and variability as well as excipients role in the drug-product supply chain[2]. A limited choice of excipients with all of these attributes are presently available in the market can make formulation design and challenge selection of excipient[3]. Hence, there has always been a search for the better pharmaceutical excipients for formulation development. Moreover, investigation of new pharmaceutical excipients is also an important tool to overcome patent curtains and cost competitiveness[4]. Therefore presently, in highly competitive and increasingly global pharmaceutical market, when there is a mounting pressure on the research and development (R&D), to shorten development time and get products to the market faster with a cost effective formulation, new pharmaceutical excipients appears to be the master key at techno-scientific level for financial planning and performance of pharmaceutical industries in developing countries[5]. There has been paradigm shift towards the utilization of various natural excipients which have previously been consumed in some form by public so that it can be classified as GRAS (Generally Regarded as Safe) and thereby reducing the cost and time for regulatory approvals. Moreover, the natural materials have been extensively used in the field of drug delivery also because they are readily available, cost-effective, eco-friendly, capable of multitude of chemical modifications, potentially degradable and compatible due to their natural origin[5]. In addition this can be a potential marketing tool in the 'herbal boom worldwide', the present day consumer look for the natural ingredients in the food drug and cosmetics as they believe that anything natural will be more safe and devoid of side effects as compared to their synthetic counterparts[6]. An increasing importance is the fact that plant resources are renewable and if cultivated or harvested in a sustainable manner, they can provide a constant supply of raw material[7]. Hence the comprised research work presents pharmacotechnical investigation of precompressed granules prepared for tablet fabrication using processed flesh of Ctrullus lannatus as a novel excipient material functionally used towards tablet disintegrant action. The Paracetamol was taken as model drug in this study.

MATERIALS AND METHODS:

Material and Instruments: Watermelon collected from open market, Poly, N-1-2-Vinyl Pyrollidone (Merck chemicals, Mumbai, India); Calcium Carbonate, Magnesium Stearate, Talc (Central Drug House, New Delhi, India), Maltodextrin (Hi- Media, Mumbai, India), Paracetamol was supplied by Merck Chemicals, Mumbai, India. Hand Blender (Koryo, KHB 5011), Homogenizer (Remi India), Vertex Mixer (SPINIX), Bulk density Apperatus (Hicon), Rotary Vacuum Evaporator (Evator Rotatory Evaporator, Medica Instruments, Ltd, India), Spray Dryer (Custom made, Biotech Park, LKO), Refrigerator (Samsung), Vacuum Oven (Hicon, India), Grinder (Philips), Sieve # 10 (B.P. Standard), Projection Microscope (Olympous), Camera (Cannon), Lab. Lyophilizer (STARTEK), U.V visible spectrophotometer (Shimadzu 1700), High Sensitivity Electronic Balance (KM-2, Deva Inc), USP– Tapped density apparatus (Electrolab, India), pH meter (LI 127, Elico Ltd, India), Mechanical Stirrer (Remi, India) and Desiccator etc.

Collection and Authentication of Fruit: Watermelon (Citrullus lanatus) fruits were purchased from fruit and vegetable market Chakarpur and the same were confirmed with University Department of Life Sciences. The watermelon being a well known fruit did not call for a voucher specimen to keep. Same lot of the watermelon collected was used in all type of drying and subsequent evaluation for study.

Drying methods: The watermelon flesh taken of and blended (Koryo KHB 5011) to liquidize the pulp, passed through sieve #10 and the strain collected was homogenized (Remi, India) and shaken in a vertex shaker (Spinix, India) so as to obtain the desired hydro-extracted biomaterial in strain and to remove undesired fruit parts. This blend filtered through a muslin cloth to have water soluble fraction which was dried to powder using different drying methods viz. direct sun drying, vacuum drying, spray drying and lyophilisation[8].

Preparation of Granules: The granules were fabricated using non-aqueous wet granulation technique with calculated requisite quantities of the drug and additives (Table 1), mixed thoroughly in a double cone mixer at 90 rpm for 15 min, and a sufficient volume of granulating agent (isopropyl alcohol) was added slowly. After enough cohesiveness was obtained, the mass was sieved though # 14 standards sieve. The granules were dried in oven at a temperature below 40°C for 30 min. re-shaped and unified through sieve # 12. Talc, magnesium stearate and aerosil were finally added as anti-adherent, lubricant and glidant[9]. The granules so prepared were used for evaluation and stored in desiccators still further use for tablet compression.

Table 1: Formulation Components of Granules

Active Medicament	Paracetamol (PCM)
Diluent	Microcrystallline Cellulose (MCC)
Binder and Adhesive	Corn Starch and PVPK-25
Test Disintegrant	Spray dried Watermelon Powder
Lubricant	Stearic acid
Antiadherent and Glidant	Talc and Aerosil
Preservatives	Methyl paraben sodium and Propyl paraben sodium

Drug Content Analysis: Accurately weighed quantity of the granules containing about 0.15 g of Paracetamol, added to 50 ml of 0.1 M sodium hydroxide, diluted with 100 ml of water, shaken for 15 minutes and added sufficient water to produce 200.0 ml. Mixed, filtered and diluted 10.0 ml of the filtrate to 100.0 ml with water. To 10.0 ml of the resulting solution added 10 ml of 0.1 M sodium hydroxide and further diluted to 100.0 ml with water. Mixed well, and the quantification of paracetamol was done by Measuring the absorbance of the resulting solution at the maximum at about 257 nm through subsequent calculations taking '715' as the specific absorbance at 257 nm[10].

Granule Strength – Pinch Toughness: The mechanical strength and friability of the prepared granules was evaluated through an empiric pinch toughness assessment which held responsible the percentage of fines in the granulation and could also provide a clue regarding optimal binder concentration.

Particle size distribution: A sieve stack comprised 6 sieves with an aperture progression Powder was loaded in the coarsest sieve of the assembled stack and nest is subjected to mechanical vibration. After 10 min, the particles are considered to be retained on the sieve mesh, then weighed the powder retained in the sieves and the respective parameters were calculated[9].

Bulk and Tapped Densities: Exactly 50 g of granules were weighed and transferred to the cylinder of Bulk Density Apparatus (Hicon). The volume occupied by the granules recorded as the bulk volume. Tapped volume was recorded after there was no further reduction in volume. Measurements were done quadruplicate and average bulk and tapped volumes were recorded. Bulk and tapped densities were computed as per the method given in USP General Chapters < 616 >[11]. The data generated were used in computing the carr's index and Hausner's ratio of starch Bulk density (LBD) and tapped density (TBD) was calculated using the formula given below[12]:

Bulk Density = Weight of the powder / Volume of packing
Tapped Density = Weight of the powder / Tapped Volume

Angle of repose: Angle of repose (è) was determined by fixed funnel method[12] and inference drawn as described under general chapters[11]. The fixed funnel and free- standing cone method employ a funnel that is secured with its tip at a given height, 'h' which was kept 2 cm above graph paper that was placed on a flat horizontal surface. With 'r', being the radius of base of conical pile:

tanè = h / r thus è = tan-1(h / r)

Table: 2: Flow Properties and Corresponding Angle of Repose

Flow Property	Angle of Repose (è)
Excellent	25-30
Good	31-35
Fair	36-40
Passable	41-45
Poor	46-55
Very poor	56-65
Very-very Poor	> 66

Carr's Compressibility Index and Hausner's ratio: The Carr's compressibility index and Hauser's ratio were calculated using tapped bulk density (TBD) and bulk density i.e loose bulk density (LBD) using the formula as showed below[12]:

Carr's compressibility index (%) = [(TBD-LBD) ×100/TBD]
Hausner's ratio = [TBD/LBD × 100]

Carr's compressibility index is a one point determination and serves as an empirical guide to Flowability and consolidation behavior of a powder It is a simple index that can be inferred through a scale of Flowability as given below in Table 3.

Table 3: Scale of Flowability

Type of Flow	Carr ' s Index (%)
Excellert Flow	5 --15
Good Flow	12 --16
Fair to Passable Flow	18 --21
Poor Flow	23 --35
Very Poor Flow	33 --38
Extremely poor Flow	>40

A similar index has been given by Hausner Values less than 1.25 indicate good flow (=20% Carr's index), while greater than 1.25 indicates poor flow (=33 % Carr's index). Between 1.25 and 1.50 added glidant normally improves flow.

Water Tr eatment Test: Granules prepared with processed watermelon powder were subjected to treatment with distilled water in a neat, clean and dry Petridis in view to assess their tendency to disperse into GI fluid. The aquatic sample was mounted on to the stage of projection microscope for direct observation of the granules undergoing deformational changes with time.

RESULTSAND DISCUSSION:

The formulation of solid dosage forms involves processing of multiparticulate powders which are heterogenous in shapes, size and size distributions. The importance of regular flow properties of powder or granules from the hopper to the die of the machine cannot be over emphasized. The need to ensure the free flow properties of powders poses a lot of challenges to the pharmaceutical formulator and hence there is a desire for pre-granulation procedure prior to further processing. Granulation is the process by which powdered particles are made to possess cohesive qualities aggregate or adhere to form regular larger sized multiparticulate entities called granules by the addition of a granulating (binding) fluid. Granulation of drug particles is usually carried out to impart cohesiveness to the tablet formulation and to improve on the flow characteristic properties of the individual particles in order to improve the inherent poor compression properties and to prevent segregation of the primarily from differences in size or density[13-12]. An important consideration which is often ignored during tablet processing is the size of the particles before compaction[15]. The goal of pharmacotechnical characterization, therefore, is to predict the desired formulation parameters of the granulations prepared for tablet fabrication through appropriate methodology which could assure to a certain extent about the suitability of powdered components used for formulation. The comprised reviled the prepared granules had normal particle size distribution in all the batches and ranges from 179.52±0.38 to 65.83 ± 0.48ìm. The formulation F42 had highest arithmetic mean diameter (ì) and F5 found with lowest arithmetic mean (ì) diameter. It is tempting to think of each particle in a granular material as a large molecule in a normal gas or liquid. This approach has problems because it is immediately apparent that the masses of the individual particles are so large that classical mechanics is all that is relevant to their dynamics and deformation[16]. Thus, the ability of an excipient to impact and control the amplitude of its implicit property is intrinsically related to the process used to generate the product[17]. Characteristics of granulation are reported to affect a lot the properties of compressed tablets manufactured[18]. A new component added or replaced in formulation may cause a cognizable difference in attributes of granulation It was therefore subjected to

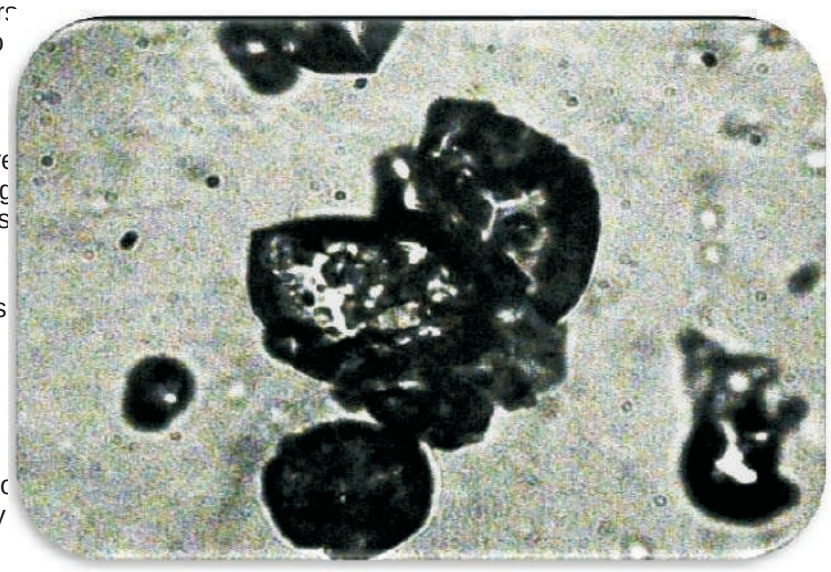

Figure 1: Photographs Immediate taken after water treatment