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REVIEW ARTICLE

Natural Binding Agents in Tablet Formulation

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ABSTRACT

Binders are agents employed to impart cohesiveness to the granules. This ensures the tablet remains intact after compression. The development of new excipients for potential use as binding agent in tablet formulations continues to be of interest. This is because different binding agents can be useful in achieving various tablet mechanical strength and drug release properties for different pharmaceutical purpose. Natural polysaccharides are widely used in the pharmaceutical and food industry as excipients and additives due to their low toxicity, biodegradable, availability and low cost. Natural binders like different starches, gums, mucilages dried fruits possess binding capacity as well as some other properties like disintegrant, filler, sustain release, and these natural polymers are much safer and economical than polymers like PVP. Different starches like rice, potato, maize, corn, wheat, tapioca starch and gums like ferula gummosa boiss, gum olibanum, beilschmiedia seed gum, okro gum, aegle marmelod gum, gum cordial, okra gum and cassia roxburghii seeds gum and plant fruit like date palm fruit and orange peel pectin shows good potency as a binding agent.

Keywords: Excipients, Binding agents, Natural Ploysaccharides, Additives, Low cost.

INTRODUCTION

The role of excipients in determining the quality of a formulation and in many cases the bioavailability of drug from tablets has received considerable attention. Binders are added to tablet formulation to impart plasticity and thus increase the interparticulate bonding strength within the tablet. The development of new excipients for potential use as binding agent in tablet formulations continues to be of interest. This is because different binding agents can be useful in achieving various tablet mechanical strength and drug release properties for different pharmaceutical purpose [12].

Binders are agents employed to impart cohesiveness to the granules. This ensures the tablet remains intact after compression as well as improving the flow qualities by the formulation of granules of derived hardness and size. The choice of a suitable binder for a tablet formulation requires extensive knowledge of the relative importance of binder properties for enhancing the strength of the tablet and also of the interactions between the various materials constituting a tablet [27].

To hold various powders together to form a tablet is a binder, fillers usually do not have good binding capacity, binder is either added in dry mix or mix in granulating liquid, binder form matrix with fillers and drug embedded in it, on drying solid binder forms glue which holds the particles together, the wet binder is the most important ingredient in the wet granulation process, most binders are hydrophilic & most times soluble in water.

Types of Binders:

Classification on the basis of their source:-

1. Natural polymers: starch, pregelatinized starch, gelatin, acacia, tragacanth and gumes.
2. Synthetic polymer: PVC, HPMC, methyl cellulose, ethyl cellulose, PEG.
3. Sugar: glucose, sucrose, sorbitol.

Classification on the basis of their application:

1. Solution binders: are dissolved in a solvent (for example water or alcohol can be used in wet granulation processes). Examples include gelatin, cellulose, cellulose derivatives, polyvinyl pyrrolidone, starch, sucrose and polyethylene glycol.

2. Dry binders: are added to the powder blend, either after a wet granulation step, or as part of a direct powder compression (DC) formula. Examples include cellulose, methyl cellulose, polyvinylpyrrolidone, and polyethylene glycol.

1. Natural polymers:

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Advantages of Natural binder [25]:

1. Natural polysaccharides are widely used in the pharmaceutical and food industry as excipients and additives due to their low toxicity, biodegradable, availability and low cost.
2. They can also be used to modify the release of drug, thereby, influencing the absorption and subsequent bioavailability of the incorporated drug.
3. They act as vehicles which transport the incorporated drug to the site of absorption and are expected to guarantee the stability of the incorporated drug, the precision and accuracy of the dosage, and also improve the organoleptic properties of the drugs where necessary in order to enhance patient adherence [30].
4. They should optimize the performances of dosage forms during manufacturing as well as when patients ingest them [29].

Disadvantage of Polymer binders [31]:

1. Polymer binders can lead to processing difficulties such as rapid over granulation. Over time they occasionally lead to tablet hardening and a decrease in dissolution performance [10,21].
2. When polymer binders are chosen, the addition of strong disintegtants such as super disintegrants is typically required but these are considerably expensive and have a negative effect on product stability as well as film coating appearance of the finished products [19].

A) Starch as binder

There are various types of natural polymers like starch, gums, pregelatinised starches are used as binding agent. Starches like rice starch, maize starch, potato starch, wheat starch, corn starch are well known for their binding and disintegrating properties but some other starches like enset starch and banana starch can also be used as binding agent. Starch is also used as fillers.

Starch is widely used as thickening, stabilizing, gelling and/or filling agent in many food applications and it considered as the most used excipient in pharmaceutical formulations. It has many pharmaceutical applications and it is used mainly in tablets as filler, binder or disintegrant [16]. Starch is the major carbohydrate reserve in plant tubers and seed endosperm where it is found as granules. It contains mainly two types of polymer molecules; several million of highly branched amylopectin molecules (normally 70-80%) accompanied by a higher number of largely linear amylase molecules (normally 20-30%) [5].Starch is one of the most widely used excipients in the manufacture of solid dosage forms. Starches from different sources have been evaluated and used as excellent binders in either mucilage or the dry powdered form. Although maize starch is the most frequently used excipient in tableting, researchers have tried to develop botanical starches for use tablet excipients.

1. Dioscorea rotundata as a binding agent:

The use of Dioscorea rotundata as a binder and disintegrant in tablet formulation and Itiola also investigated the compressional properties of this particular starch [17]. The effects of pigeon pea and plantain starches on the compressional, mechanical and disintegration properties of Paracetamol tablets have been investigated [18]. The role of ginger starch as binder in acetaminophen tablets was found.

2. Starch 1500 as a binding agent:

Starch 1500 performed as an excellent binder producing a granulation that was compressible and produced Lamivudine tablets of improved hardness and friability compared with those prepared with povidone. The formulation of Lamivudine tablets with Starch 1500 exceeded the disintegration and dissolution performance of the povidone formulation that utilized a super disintegrant [31].

The nature and amount of the binders were found to alter the disintegration and dissolution rates of the tablets by reducing their wet ability as measured by the adhesion tension of water. During pharmaceutical granulation, the objective is to produce granules that have a uniform (and repeatable) distribution of drug particles within the bulk carrier (excipient) solid [15]. This can be difficult to achieve and both drug depletion and enrichment in granules can occur [37]. A linear relationship has been found to exist between the adhesion of water on the tablets and their disintegration and dissolution rates.

3. Tapioca starch as a binding agent:

The use of a natural product tapioca starch as binding agent in the formulation of Diclofenac tablets was identified. To establish two other commonly used disintegrating agents potato starch and maize starch were selected and formulated for comparison. Different formulations were prepared by using above three disintegrants in the concentration of 20mg per tablet. The tablets were prepared by wet granulation technique. All the formulations were subjected to in in-vitro evaluation and the results were compared. The nature and amount of the binders were found to alter the disintegration and dissolution rates of the tablets by reducing their wet ability as measured

by the adhesion tension of water. During pharmaceutical granulation, the objective is to produce granules that have a uniform (and repeatable) distribution of drug particles within the bulk carrier (excipient) solid. This can be difficult to achieve and both drug depletion and enrichment in granules can occur. A linear relationship has been found to exist between the adhesion of water on the tablets and their disintegration and dissolution rates [1].

Extraction of different starches:

1. Extraction of tapioca Starch:

The starch was extracted from root tubers of cassava (Manihot esculenta) according to the method of Alebiowu [1] using established procedures . Cassava tubers were peeled, washed and cut to small pieces. These small pieces were then soaked in distilled water for specified period of time i.e. for 1 h. At the end of the steeping period, the softened tubers were milled to a pulp, and more distilled water was added to give dilute slurry which was sieved using mesh size 100 [1].

2. Extraction of rice starch:

Starch isolation by neutral protease used rice flour (100 g, as is) mixed with deionized water (200 mL) in a 500-mL reaction beaker. The temperature was maintained at 50°C with a circulator, and the slurry pH was adjusted to 7.0 with 1.0 N NaOH. Different levels of neutral protease (0.01, 0.03, or 0.05% on rice flour basis) were added to the slurry and reacted for 1, 3, or 5 hr with constant stirring using a magnetic stirrer. The flour slurry was then blended with a Waring blender at a high speed for 2 min after the protease digestion. The slurry was passed through a 63-m screen and centrifuged at 1400×g for 10 min. The starch layer was reslurried and washed with deionized water 3 times. The isolated starch was dried at 45°C for 48 hr [35].

3. Extraction of corn starch:

Stage 1 consisted of crushing the dry kernels with a hammer, removing the seed coat, separating the germs, and collecting the starch without drying it under the fan.

Stage 2 is briefly described in three steps:

(a), three corn kernels were placed in screw-top 25-ml test tubes. Sodium meta-bisulfite 0.45% (2 ml) were added to each tube before incubation in a 50°C water bath for 48 hr (± 2 hr) to soften the kernel, enhance peeling of the seed coat, and preserve the kernel during steeping.

(b), after incubation, the sodium metabisulfite was decanted and the seed coat and germ were manually removed from the kernels. A mortar and pestle was used to grind endosperm as fine as possible.

(c), the resulting starch was dried in front of the fan overnight [36].

4. Extraction of potato starch:

Enzyme solution was prepared by mixing thoroughly 1g of the enzyme in 10ml of distilled water by a glass rod in a 20ml test tube. The potatoes were washed under tap water so that any dirt adhered to it may be removed. After washing the potatoes were cut into small pieces without peeling with a stainless steel knife to facilitate grinding. Grinding was done in Commercial (Sumeet) grinder having motor rpm of 15000 for 1 min and 15 s after standardizing the time. The ground potato meal was then transferred to a 500 ml conical flask and appropriate amount of water was added to the meal. The prepared enzyme solution was added to the potato meal using a pipette. For concentration of 0.1g per 100g of potato meal, 1ml of the enzyme solution was added to 100g of potato meal. The flask was cotton plugged and kept in incubator cum shaker at 45°C with a shaking speed of 125 rpm. The pH of all the samples varied between 6 and 7 and cellulase enzyme is effective between pH 3 and 7. So, the natural pH of the broth was not changed. After incubation the resultant slurry was screened by a nylon tea strainer of mesh size of 100 into a 400 ml beaker. During screening the pomace was washed two times in 150 ml of tap water. Sedimentation was done for 1 h to separate the starch from the other components of the filtrate containing starch [23].

5. Extraction of wheat starch:

Starch was isolated from flour using a modified protein digestion procedure [7, 22] from wheat flour (12.1% protein; 13.0% moisture content). Flour (0.3 g) was placed in 50-mL plastic centrifuge tubes with 5.0 mL of water and 2 mL of 0.8% pepsin A (P7012, Sigma, St. Louis, MO) in 0.04N HCl and incubated for 60 min at 37°C. After protease treatment, 1.0 mL of 0.08% Hemicellulase 90 (90,000 U/g activities, a gift from Amano Enzyme U.S.A., Lombard, IL) in 0.1M sodium acetate buffer (pH 4.5) was added to the mixture and incubated for 3 hr at 45°C. A detergent mix (1 mL) (5% SDS, 5% Triton X-100, 5% Tween 40, and 5% Triton X-15) was added after incubation, and the suspension was vortex-mixed for 30 sec. The enzyme-treated starch was centrifuged at 2,500 rpm for 5 min in a Sorval SS-34 rotor and SS-3 centrifuge. The starch was washed twice with water; the supernatant was discarded and the starch pellet was resuspended in

5 mL of water followed by vortex mixing for 30 sec and centrifuging at 2,500 rpm for 5 min. A final water wash was conducted in a microcentrifuge tube with 1.0 mL of water and centrifuged for 1 min [6].

B. Natural Gums as binder:

The development of new excipients for potential use as binding agent in tablet formulations continues to be of interest. This is because different binding agents can be useful in achieving various tablet mechanical strength and drug release properties for different pharmaceutical purpose. In recent times, increasing attention has been given to the application of gums of various sources as pharmaceutical excipients. Gums generally are polysaccharides which are polymeric in nature of natural substances obtained from woody and non-woody plant parts such as bark, seeds, sap, roots, rhizomes, fruits and leaves. Plant gums are widely used in diverse applications for the formulation of pharmaceutical dosage forms. The major application of gums is in tablets as binding agent [12].

1. Ferula gummosa Boiss as binding agent:

Ferula gummosa Boiss is one of the natural plants of Iran. The whole plant, but especially the root, contains the gum resin igalbanumi. Enauyatifard et al studied the comparative effects of galbanum gum and two standard binding agent n polyvinylpyrolidone and acacia on characteristics of acetaminophen and calcium carbonate compacts was made. The Ferula gummosa gum was extracted and its swelling index was determined. Acetaminophen and calcium carbonate granules were prepared using the wet granulation method and were evaluated for their micromeritics and flow properties, while the compacts were evaluated for mechanical properties using the hardness, tensile strength and friability. The drug release from acetaminophen compacts were assessed using dissolution studies. Ferula gummosa Boiss (Apiaceae) is a perennial plant native to central Asia, growing in the northern and western parts of Iran. The whole plant, but especially the root, contains the gum resin igalbanumi. Several medicinal actions such as anticonvulsant, expectorant, antispasmodic and anticatarrah have been reported for F. gummosa plant and its gum. Externally, it is used as a plaster for inflammatory swelling, ulcers, boils, wounds and skin complaints. Numbers of schizogenous ducts of F. gummosa are in the cortex containing the resinous gum.

2. Gum olibanum as binding agent:

The binding properties of mucilage extracted from Gum Olibanum [3]. The main objective of the current study is to exploit the use of Gum Olibanum as natural binding agent in development of oral tablet formulations taking Fruosemide as model drug. Some of the mucilage has also been used in tablet formulations as binding agent also to sustain the drug release [34]. Natural mucilage are nontoxic, non irritant and act as stabilizers, emollients and stiffening agents [9].Gum Olibanum mucilage was evaluated for its granulating and binding properties in tablets, using furosemide as a model drug. Mucilage was used in different concentrations of 5.7 and 10 % w/v. The granules were prepared by wet granulation technique (Awen et al 2010) [3].

3. Beilschmiedia Seed Gum as Tablet Binder:

The Beilschmiedia gum was isolated from the edible seeds of Beilschemiedia mannii (family Lauraceae) and evaluated for its binding properties at a concentration range of 0.5- 10 % w/w in paracetamol tablets with official gelatin as a control [9]. A comparative analysis was conducted that shows the granules bound with Beilschmiedia gum were relatively bigger and harder than the ones obtained with gelatin gum. The hardness, disintegration time and dissolution rate increased with increase in concentration of Beilschmiedia gum. Tablets containing 5 % w/w of Beilschmiedia gum had a binding capacity approximately twice that of gelatin with a dissolution rate of 91 % after 30 min. They concluded that Beilschmiedia gum possesses potential as a commercial binding agent [13].

4. Okro gum as tablet binder:

The okro gum is suitable as a binder for pharmaceutical tablet formulations. A comparative evaluation of Abelmoschus esculentus (okro) gum as a binder in the formulation of thiamine hydrochloride granules and tablets was performed [17]. Gelatin, acacia and polyvinylpyrrolidone (PVP), were employed as standard binders for comparison. The properties of granules and tablets evaluated were; flow rate, angle of repose, density, weight uniformity, hardness, friability, disintegration time and dissolution rate. The granules had good flow properties. However, binder concentration influenced flow characteristics. Okro gum gave the highest hardness/friability ratios. It also prolonged disintegration time and dissolution time and dissolution rate. Hence, okro gum may not be useful as a binder in conventional tablet formulation. Onunkwo concluded that okro gum could be a good candidate for evaluation as a

binder or hydrophilic polymer in sustained release tablet formulation [26].

5. Aegle marmelos Gum as Tablet Binder:

The oral tablet of paracetamol was formulated by using Aegle marmelos fruit gum as a binder. The four different tablet formulations were prepared by wet granulation method [19]. The binder concentrations used in the formulation were 2, 4, 6 & 8 % w/w of cordia fruit gum; tablets were subjected for evaluation of hardness, friability, drug content uniformity. Preliminary evaluation of granules showed that, 0.71 to 0.77 mm granule size, 29.20 to 30.10º angles of repose and 22.1 to 12.7 % fines. Hardness was found to be in the range of 7.1 to 7.4 kg/cm^2, the percent friability was in the range of 1.50 to 0.75 %, and tablet showed 97.46 to 98.96 % of labelled amount of paracetamol indicating uniformity in drug content, 8 to 18 min disintegration time and more than 90% dissolution in 75 min. Tablets at 6 % w/w binder concentration showed more optimum results as tablet binder. Patil concluded that the Aegle marmelos gum was found to be useful for the preparation of uncoated tablet dosage form.

7. Gum cordial as tablet binder:

Dinda studied the toxicity and chemical compositions of the cordial gum and gum tablet excipient interactions using FTIR (Fourier transform infrared) spectrum ensured its safe use as a tablet binder. Tablets were manufactured with various quantities of cordia obliqua fruit mucilage as tablet binding agent and a comparison was made against the tablets prepared with 5% starch paste as binder, based on studying the standard parameters like hardness, thickness, friability, weight variation and disintegration time. Gum cordia at a very low amount (1/25th of the starch paste used) was found to be effective as tablet binder. Thus this gum will be a non-toxic, bio- degradable, cheap, economic and easily available option as tablet binder and emulsifier in the list pharmaceutical excipients [11].

6. Okra gum as a tablet binder:

The aim of this study was to evaluate the effectiveness of a new binder extracted from Hibiscus esculentus (Okra gum) in tabletting. Okra gum was extracted from the pods of Okra fruit by maceration in distilled water followed by filtration of viscous solution as well as precipitation of gum extract by using acetone. To evaluate the binder effectiveness, two models, including a placebo formulation (lactose) and a drug formulation (Acetaminophen, Ibuprofen, and/or Calcium acetate) were evaluated. Granules were prepared by different concentrations (0.5-6 %w/w) of Okra gum and tabletted using a Kilian single punch press. Cornstarch (12.5 % w/w) and P.V.P (22 %w/w) were employed as the standard binders for comparison [33].

8. Cassia Roxburghii seeds gum as tablet binder:

Girhepunje found the Cassia roxburghii seed gum for its binding property. And isolated gum from Cassia roxburghii seed, was evaluated for its binding property like % of fine, stability and viscosity. The adhesive and cohesive property in tablet like hardness, friability, disintegration time and dissolution rate were evaluated on paracetamol tablets. All evaluations were compared with widely used standard sodium carboxy methyl cellulose and gelatin. The gum is prepared from seeds of Cassia roxburghii and the prepared gum was evaluated in different concentration like 1%, 1.5% and 2% which compared with the same concentration of sodium CMC and gelatin. The Cassia roxburghii seed gum was found to be more viscous than sodium CMC and gelatin. Which also produce fewer fines. Only the marginal difference was found in the hardness of tablet when compared with standard sodium CMC and gelatin. It also showed linearity between concentration and hardness. Increased concentration of Cassia roxburghii seed gum from 2 to 6% increased the disintegration and dissolution time. Cassia roxburghii gum produce tablet with better mechanical property longer disintegration and dissolution time than those containing sodium CMC and gelatin. This suggestthat Cassia roxburghii gum could be useful binding agent especially when high mechanical strength and slower release concern [14].

Extraction method of different gums:

1. Extraction of gum galbanum:

The powdered dried galbanum (200 g) was macerated in distilled water (100 mL) at 50OC and shaked for 30 min, and then the mixture was stirred for 24 h. The mixture was filtered and the filtrate was concentrated to dryness and weighed [12].

1. Extraction of Gum olibanum:

The gum was isolated from plant and then treated with a mixture of chloroform and water in ratio of 5:95 for 5 days with occational mixing. Any extraneous materials are then filtered and the gum is then precipitated by adding absolute ethanol. The precipitated gum was filtered, washed with ether and air dried. The dried gum was powdered and passed through 100 mesh for further use [4].

2. Extraction of Beilschmiedia gum:

Beilschmiedia gum was collected from a local farm in Ijebu-Itele in Ogun State, seeds were sun dried, crushed using a mortar and pestle and pulverized in a blender (Model 857, Chrome white, Osterizer, U.S.A.) to produce the gum powder. The gum powder was sifted (sieve size 150 μm) and hydrated in double strength chloroform-water mixture for 5 days with intermittent stirring. The resultant mucilage was screened through a clean calico cloth to remove extraneous materials and undissolved gum. The pure gum was precipitated from solution with 95 % v/v ethanol in the ratio of 2:3 for gum and 95 % v/v ethanol respectively. The precipitated gum was filtered and washed with diethyl ether and dried in a hot air oven at 400 C for 24 h [13].

3. Extraction of gum Okro fruit mucilage:

One kg quantity of unripe and tender fruits of okro gum was used. The fruits were washed, sliced and ground by means of a blender. The crushed mass was soaked in distilled water to hydrate with occasional stirring six hours. A white muslin cloth was used to express the viscous solution to produce the gum extract. Acetone was used to precipitate the extract at a ratio of 3 parts of acetone to 1 part of extract. Filtration of the precipitated gum was performed using a vacuum pump, attached to a Buckner funnel with filter paper (Whatman, 12.5 mm). Finally, the gum was dried in a desiccator containing anhydrous calcium chloride. Size reduction and screening of the dried gum was carried out using an end runner mill, and a 250 m stainless steel sieve [26].

4. Extraction of gum Aegle marmelos:

Fresh white gum of Aegle marmelos was collected from authenticated plant fruits. The well dried gum was powdered in mortar, passed through sieve no.80 and solublised in distilled water. The concentrated solution was precipitated in acetone. The precipitate was separated and dried at 60^0 C [28].

5. Extraction of gum Okra fruit mucilage:

Okra gum was extracted from the pods of Okra fruits. The fruits were cleaned, washed, sliced, crushed and then macerated in distilled water for 10 hours with intermittent stirring. The mucilage was filtered through a white muslin cloth to extract the gum and acetone was added to precipitate the extracted gum. The gum was then filtered under vacuum to remove acetone and dried in desiccators [33].

6. Extraction of Cassia Roxburghii seed gum:

The seeds of C. roxburghii were coarsely powdered, defatted by soxhlet extraction using petroleum ether (60-800 C).Then extracted mucilage was precipitated with acetone and freeze dried to get fine gum powder. Yield was found to be 24% [14].

C. Dried fruits as binding agent:

1. Date palm fruit as a binding agent:

Dried and milled date palm fruit was evaluated for its binding properties in comparison with acacia and tragacanth. Characterization of the granules in addition to quality control tests that included uniformity of weight, hardness, friability, disintegration and dissolution were undertaken. The granules manufactured using the binders had good flow properties and compressibility. As the concentration of the binders increased, the binding ability improved producing tablets with good uniformity of weight and hardness. The tablets manufactured using dried date palm was found to be less friable than tablets manufactured using acacia and tragacanth [25].

2. Orange peel pectin as binding agent:

The aim of present study was to extract pectin from dried orange fruit peels and assess its binding property in tablets using ibuprofen as a model drug. Extraction of pectin was carried out by microwave assisted extraction technique and pectin was isolated using acetone as a precipitating agent. Three different batches of tablets were formulated using pectin in different proportions (10, 20, 30 mg) and to compare the binding property of pectin, a reference batch was also formulated using starch as a binding agent instead of isolated pectin. Pre-compression and post-compression evaluation studies were performed for all formulations and found to be within the range as prescribed in the pharmacopoeias [20].

Extraction of pectin:

Extraction of pectin from dried orange fruit peel was carried out by microwave assisted extraction technique. 25 g of dried orange peel was cut into small pieces and soaked in 200 ml of distilled water for 2 h in a 1000 ml beaker. Its pH was adjusted to 4.5 by using 10 % tartaric acid solution and subjected to microwave irradiation at 160 W for 10 min. It was then filtered while hot; filtrate was cooled and poured into a beaker containing 600 ml of acetone to precipitate out pectin. The precipitated pectin was then separated by vacuum filtration and washed with acetone to make the pectin free from acidic ions. Pectin thus obtained was completely dried at 37º C in a hot air oven [20].

CONCLUSION

There are large numbers of natural polymers have been used in pharmaceutical preparations. Natural substances like starches, mucilages, gums and also dried fruits can be used as binding agent. They have been shown good potential as binding agent as well as they posses some other properties like disintegrating agent, fillers, sustain releasing agent. Natural polymers shown good binding property in wet granulation, granules are stable and less friable in comparison with other binders. They can also be used to modify the release of drug, thereby, influencing the absorption and subsequent bioavailability of the incorporated drug. Furthermore, they act as vehicles which transport the incorporated drug to the site of absorption and are expected to guarantee the stability of the incorporated drug, the precision and accuracy of the dosage, and also improve on the organoleptic properties of the drugs where necessary in order to enhance patient adherence. They should optimize the performances of dosage forms during manufacturing as well as when patients ingest them.

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