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CHARACTERIZATION OF A NOVEL COPROCESSED POWDER OF *LENTINUS TUBER REGIUM* AND POLYVINYLPYROLLIDONE (POVILENT)

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ABSTRACT

This study was aimed to formulate and characterize a novel coprocessed excipient (Povilent) from processed *Lentinus tuber regium* (LTR) and polyvinylpyrollidone (PVP) to improve the flowability and compressibility of LTR. Povilent was produced by blending and co-drying alcoholic dispersions of LTR and PVP powders (70: 30 % w/w). The physico-technical properties of the new powder namely: bulk, tapped and particle densities, angle of repose, flow rate, Carr's index, Hausner's ratio, pH, swelling index, hydration capacity and dilution potential were determined in comparison with those of the natural and processed powders of LTR. Results show that the bulk and tapped densities increased insignificantly from the natural to the coprocessed excipients (Povilent> Processed LTR >Natural LTR) ($P>0.05$) while those of the particle density was very significant ($P<0.05$). On the other hand, the angle of repose, Carr's index, Hausner's ratio and porosity decreased from the natural to the coprocessed excipients (Natural LTR > Processed LTR >Povilent) ($P<0.05$). Swelling index was in the order: Natural LTR >Povilent> Processed LTR, though insignificant ($P>0.05$), while the hydration capacity took the order: Natural LTR > Processed LTR >Povilent ($P<0.05$). Povilent has a dilution potential of 70-90% (paracetamol), 20-30% (ascorbic acid and metronidazole) respectively. The compacts prepared from both the processed or natural LTR were very friable. Flowability was highly improved in Povilent than the processed powder alone, the natural form not flowable.This shows that the flowability and compressibility of LTR was highly improved by coprocessing it with PVP.

Keywords: Characterization, novel, coprocessed, powder, *Lentinus tuber regium*, polyvinylpyrollidone, povilent.

INTRODUCTION

Pharmaceutical excipients as raw materials have multi-sources such as natural or synthetic. The major targets of researchers in pharmaceutical technology and industrial pharmacy include the introduction of new and better excipients, drug raw materials, formulations and equipment in laboratory pilot scale-up and commercial production of pharmaceutical dosage forms [1]. Several natural raw materials are available as polymers. They are synthesized with chemicals obtained from petroleum, etc. Synthetic polymers, though useful industrially, are not environmentally friendly due to their non-biodegradability. Majority of natural polymers are polysaccharide gums and they are non-toxic to humans and are readily metabolized in the body [2]. Excipientswith improved functionality can be obtained by developing new chemical excipients through combinations of existing materials [3]. This has been the most successful strategy for the development of new excipients in the past decades [4]. It has been supported by the introduction of better performance grades of excipients such as pregelatinized starch, croscarmellose and crospovidone. However, functionality can be improved only to a certain extent because of the limited range of possible modifications [5].One of the ways to obtain new pharmaceutical excipients is by particle engineering.

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A much broader platform for the manipulation of excipient functionality is provided by coprocessing or particle engineering of two or more existing excipients [6]. Coprocessed excipients are prepared by incorporating one excipient into the particle structure of another using process such as co-drying [7]. The coprocessed multi-component-based excipients are introduced to achieve better characteristics and tableting properties than a single substance or the physical mixtures [8]. These have been developed primarily to address the issues of flowability, compressibility and disintegration potential. Several of these excipients are commercially available e.g. ludipress (lactose, polyvinylpyrollidone and crosspovidone), cellactose and microlac (lactose and cellulose), starLac (starch and lactose), prosolv (microcrystalline cellulose and silicon dioxide) [9,10]. Material science plays a significant role in altering the physico-mechanical characteristics of a material, especially with regard to its compression and flow behaviour. Coprocessing of excipient offers an interesting tool to alter these physico-mechanical properties. It is generally conducted with one excipient that is plastic and another that is brittle. Maarschalk reported coprocessing performed with a large amount of brittle material and a small amount of plastic material, as exemplified by cellactose (Meggle Corp.) in which 75% lactose (brittle material) was coprocessed with 25% cellulose (plastic material) [11]. A combination of plastic and brittle materials is necessary for optimum tableting performance. Such combinations can help improve functionalities such as compaction performance, flow properties, etc. The primary attribute associated with these excipients is that no chemical change exists during coprocessing and all the reflected changes show up in the physical properties of the excipient particles [12]. Another advantage achieved with coprocessing is improved flow properties due to controlled optimal particle size and particle-size distribution [13]. Coprocessed excipients have been used mainly in direct-compression tableting because in this process there is a net increase in the flow properties and compressibility profiles and the excipient formed is a filler-binder. The compressibility performance of excipients such as cellactose [14] and ludipress [15] have been reported to be superior to the simple physical mixtures of their constituent excipients. Coprocessed powders enjoy better dilution potential, fill weight variation and reduced lubricant sensitivity. The plastic material provides good bonding properties because it creates a continuous matrix with a large surface for bonding while the brittle material provides low lubricant sensitivity because it prevents the formation of a coherent lubricant network by forming newly exposed surfaces upon compression, thus breaking up the lubricant network. Major limitations of co-processed excipient is that the ratio of the excipients in a mixture is fixed and in developing a new formulation, a fixed ratio of the excipients may not be an optimum choice for the active pharmaceutical ingredient and dose per tablet under development [16].

This study was aimed to formulate and characterize a novel coprocessed excipient (Povilent) from processed *Lentinus tuber regium* (LTR), an edible mushroom (brittle and incompressible) and polyvinylpyrollidone (a binder and plastic material) to improve the flowability and compressibility of LTR. The technique of co-drying was used in the preparation of these new coprocessed excipients. The physico-technical properties of the new excipient weredetermined along those of the natural and processed forms of LTR and their results were considered to ascertain the extent of improvement on the flowability and compressibility of LTR through coprocessing. There was no literature on coprocessed powder of LTR and PVP. It is believed that the new excipient may be beneficial as a filler-binder and disintegrant especially in direct compression tableting technology.

Lentinus tuber regium is a basidiomycete which grows wildly in the tropical and subtropical regions of the world [17,18]. It has been successfully grown in the laboratory [19,20]. The sclerotium is often dark brown on the surface and white inside. Its most dietary application in Nigeria is as a soup thickener. The white tissue when blended and added to soup swells and adds bulk to the soup. It is this swelling characteristic of *L. tuber-regium*which has advised the investigation into the possible use of this non-toxic basidiomycete as a tablet disintegrant by Iwuagwu and Onyekweli, using paracetamol granules prepared by wet granulation [21].

MATERIALS AND METHODS

All materials were used as received and include polyvinyl pyrollidone K30 (PVP), magnesium stearate, paracetamol (BoaiNky, China), 3.85% sodium hypochlorite (Reckit& Benckiser, Lagos, Nigeria), 95% ethanol, n-hexane (Sigma-Aldrich, USA). *Lentinus tuber-regium* (LTR) was procured from *eke-ututu* market in Orsu Local Government Area of Imo Sate, Nigeria.

Identification of *Lentinus tuber-regium*

The sample used for this study was identified by a Taxonomist, Dr. N. L. Edwin-Wosu, University of Port Harcourt reference herbarium as: *Lentinus tuber-regium* (fr.) (family: Polyporaceae); Syn. *Pleurotus tuber-regium* (fr.). It was assigned a voucher number: OG-Acc-001. UPH. No C-058 and it was deposited in the University of Port Harcourt, Port Harcourt, Nigeria herbarium.

Processing of *Lentinus tuber-regium* powder

The ***Lentinus tuber-regium*** **powder** was processed as described by Iwuagwu and Onyekweli [21]. The dark brown skin of the sclerotia was peeled off and the white tissue cut into small pieces. It was ground intocoarse powder in a dry electric mill (Binatone, China).

It was further micronized in a ball mill (Erweka, D-63150, Germany). The fine white powder was bleached whiter by submerging it in 3.85% w/v sodium hypochlorite with continuous stirring for 30 min. The submerged powder was washed severally with deionized water to free it from the bleaching agent. The wet material was slurred with 95% ethanol in a stainless steel vessel and left to stand in a water bath at a temperature of 60^{o} C with continuous stirring for a period of 60 min. The slurry was then squeezed using a fine muslin cloth. This process was meant to hasten drying. The wet mass obtained was dried in hot air oven (New life DHG-9023A, China) at 60 ^{o} C for 23 h.The resulting powder was passed through 180um sieve (Endecott, England) and stored in airtight amber coloured bottle.

Coprocessing of processed *L. tuber regium*and polyvinyl pyrollidonepowders

The new coprocessed powder was obtained by combining 70% w/w of processed LTR powder with 30 % w/w of PVP. Alcoholic dispersion of each was prepared separately and later, both were blended with an electric blender for 10 min. It was transferred into a glass beaker and stirred until the alcoholic content evaporated. The damp mass was granulated with sieve number 18 (1.00 mm). The granulate was dried to constant weight in a hot air oven at 50^{o} C. The dry granules was classified using a 250µm stainless steel sieve and stored in an airtight amber coloured glass bottle.

Characterization of the coprocessed powder

The physico-technical properties of the coprocessed powder were determined alongside those of the natural and processed LTRto determine the extent of improvement in flowability and compressibility of LTR through this research effort.

Densities

A 20 g quantities of the respective powders was employed in the determination of bulk and tapped densities using Stampfvolumeter (STAV 2003JEF, Germany). Three replicate determinations were carried out for each powder. The particle densities of the respective powder were also determined by displacement method using a 25 ml pycnometer and n-hexane as a non-solvent. The weight of the pycnometer (w) wasdetermined (Metler, Germany). The pycnometer was later filled with n-hexane and reweighed (w_1). The weight of n-hexane (w_2) was obtained by subtracting wfrom w_1. A 0.5 g (w_3) of powder was introduced into the pycnometer containing n-hexane and weighed (w_4). The densities of the respective samples were calculated from the following equations:

$$\text{Bulk density} = \text{Weight of powder}/\text{Bulk volume} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots (1)$$

$$\text{Tapped density} = \text{Weight of powder}/\text{Tapped volume} \quad \ldots\ldots\ldots\ldots\ldots\ldots (2)$$

$$\text{Particle density, } \rho t = w2 \times w3/v(w3 - w4 + w2 + w) \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots (3)$$

where: v is volume of pycnometer, 25 ml

Flow parameters

A 50 g each of the respective powders was used to determine flow rate using the funnel method reported by Carstensen and Chan [22]. The angle of repose for the natural powder of LTR was determined by pouring 50 g of powder into a cylindrical paper roll fixed on to a flat base whose diameter is known and the same as the internal diameter of the cylinder. The cylinder was slowly pulled out vertically so as to form a cone of powder on the base. The height of the cone was measured. This is a modification of the method of Jones and Pilpel [23]. For the processed and coprocessed powders of LTR, their respective angle of repose was determined as follows. A clean glass funnel was clamped on a retort stand such that a constant perpendicular height of the tip of the funnel was 3 cm from a horizontal flat base with a clean graph sheet of paper. Each of the powders was in turn poured into the funnel until the powder heap formed touched the funnel tip and stopped further outflow of powder from the funnel orifice [24]. The diameter of the circumference of the heap was measured.Compressibility indexwas calculated from the relationship between bulk and tapped densities using the equation [25].

Calculations were made as follows:

$$\text{Flow rate} = \text{Mass of powder} / \text{Time} \quad \ldots\ldots\ldots\ldots\ldots\ldots (4)$$

$$\text{Angle of repose, } \theta = \tan -1 \frac{2h}{d} \quad \ldots\ldots\ldots\ldots\ldots\ldots (5)$$

where θ is angle of repose, h is height of heap powder, d is diameter of heap of powder

$$\text{Compressibility index} = \text{Tapped density} - \text{Bulk density}/\text{Tapped density} \ X100 \quad \ldots\ldots\ldots (6)$$

Hausner`s ratio was calculated from the relationship between bulk and tapped densities using the equation [26]

$$\text{Hausner's ratio} = \text{Tapped density}/\text{Bulk density} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots (7)$$

Porosity was calculated from the relationship between the bulk and true densities using the equation:

$$\text{Porosity} = [1 - (\text{Bulk density}/\text{True density})] \ x100 \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots (8)$$

Measurement of pH

The pH of 10 % (w/v) aqueous dispersion of the respective powders was determined using a pH meter (PHS - 25, China).

Solubility

The solubility of the respective powders was determined in water, alcohol, acetone, methanol, n-hexane and chloroform.

Swelling index

The swelling index of the respective powders was determined by a modification of the methods of Iwuagwu and Okoli [27]. The tapped volume, Vx occupied by 5g of each powder was recorded. The sample was dispersed in 42.5 ml of water and the volume was made up to 50ml. It was left to stand for 24 h after which the volume of sediment, Vv was noted. The swelling index was calculated from the equation:

$$\text{Swelling index} = Vv/Vx \quad \ldots\ldots (9)$$

Hydration capacity

The hydration capacity or water retention of the respective powders was determined by the method of Ring [28]. A 1.0 g quantity of each of the respective powders was placed in three separate centrifuge tubes and each covered with 10 ml of water. Each tube was shaken intermittently over a period and left to stand for 30 min. They were later centrifuged for 10 min at 3000 rpm. The supernatant was decanted and the weight of the powder after water uptake and centrifugation, *x* was determined for each powder.

$$\text{Hydration capacity} = x/y \quad \ldots\ldots (10)$$

where*x* is the weight of the moist powder after centrifugation and *y* is the weight of the dry powder.

Differential Scanning Calorimetry

The melting temperature of the respective powders was determined using a Differential Scanning Calorimetry (DSC) equipment (NETZSCH DSC 204F1, Germany).

Dilution potential of the coprocessed powder

The dilution potential of the coprocessed powder was determined using paracetamol, ascorbic acid and metronidazole. Drug and coprocessed powder was blended in proportions of 1:9 - 9:1 respectively. Each admixture was lubricated with 0.1% (w/w) magnesiumstearate prior to compression. A single punch tableting machine (CadmachMachinary, India) was used, applying a maximum compression force of 49kN. The hardness of the respective batches of compressions was determined using a digital hardness tester (Erweka TBH 100, Germany).

RESULTS AND DISCUSSION

The results of the physico-technical tests carried out are presented in Table 1. The colour of the natural, processed and coprocessed powders were off-white, white and off-white respectively. The respective powders were neither soluble in water nor any organic solvent. Dispersion was rather observed in the respective solvents. The highest yield after preparation was obtained in the coprocessed powder. Two melting peaks were observed in each of the DSC thermograms for the natural, processed and coprocessed powders as follows: 259.8/316.5, 256.9/ 301.1 and 254.0/316.8^{o}C respectively. A consistent slight reduction in melting temperature was observed from the natural, processed and then the coprocessed powder. The second peak for the coprocessed powder reverted to almost 316.5^{o}C as in the natural powder and appeared exothermically though it was endothermic in the natural powder (Figures 1-3). The changes in the melting peaks observed for the coprocessed powder may be attributed to the introduction of PVP into LTR. Results of micromeritic studies show there was no flowability in the natural powder of LTR. However, this got improved after processing of LTR and much improvement in flow rate was recorded after coprocessing it with PVP ($P<0.05$).

The particle, bulk and tapped densities appeared to increase from the natural to the coprocessed excipients, but statistically, these increases were only significant in the particle density ($P<0.05$). On the other hand, the angle of repose, Carr's index (CI), Hausner's ratio (HR) and porosity decreased from the natural to the coprocessed excipients ($P<0.05$). The angle of repose is useful to the flow properties of solids which relates to its inter-particulate friction of resistance to movement between particles [29]. Although there is some variation in the qualitative description of powder flow using the angle of repose, much of the pharmaceutical literature appears to be consistent with the classification of Carr [22,25].By this classification, materials that possess angle of repose of 25-30^{o} have excellent flow property. Those with values of 31-35^{o} have good flow and the ones with values of 36-40 ^{o} are said to have fair flow properties. When 50^{o} is exceeded, the flow is rarely acceptable for manufacturing purposes.

The CI and the HR are the simple, fast and popular methods of predicting powder flow characteristics. The former has been proposed as an indirect measure of bulk density, size and shape, surface area and cohesiveness of materials since all of them influence the compressibility index. A powder or solid material with CI < 10 % and HR of 1.00-1.11 is said to have excellent flow, CI of 11-15% and HR of 1.12-1.18 describes a solid that has good flow characteristics, CI of 16-20 % and HR of 1.19 -1.25 describes a powder with fair flow properties. Finally, CI >21% with HR > 1.26-1.34 describes powders with poor flow properties. From these analyses, the Povilent exhibited a better flow property than the natural and processed forms of LTR. The results obtained from the powder flowability studies show that the flow of LTR has been improved by

coprocessing it with PVP since though, the processed form flowed, but the natural lacks any attribute of flowability (P<<0.05). Similar enhancement in flow properties of excipients has been obtained by coprocessing techniques. Several instances include the improved powder properties in cellactose, microcellac, starLac, ludipress and microcrystalline cellulose starch. Their compressibility and flowability were better than their original components [26-33]. The changes observed in the swelling index after processing and coprocessing were statistically insignificant (P<0.05). This means that the procedures of processing and coprocessing did not affect the tendency of the material to swell. Hydration capacities of the *L. tuber regium* powder decreased consistently after processing and coprocessing respectively (P<0.05). Outcomes of dilution potentials studies show a dilution potential of 70-90% for paracetamol, 20-30% for ascorbic acid and 20-30% for metronidazole. This shows that the new excipient will be useful for direct compression of ascorbic acid or metronidazole tablet formulations.

Table 1: Physico-technical properties of the natural, processed and coprocessed powders

Property	Natural LTR	Processed LTR	CoprocessedPowder
Colour	Off-white	White	Off-white
Yield (%)	89.00	70.00	92.20
Flow rate (g/sec.)	No free flow	12.37	21.5± 0.55
Angle of repose (^{o})	53.9˚± 2.00	32.30˚±1.00	27.45˚±1.00
Particle density (g/cm^3)	1.21 ± 0.06	1.47 ± 0.09	1.48 ± 0.08
Bulk density (g/cm^3)	0.31±0.12	0.43 ±0.13	0.49±0.11
Tapped density (g/cm^3)	0.48±0.14	0.56±0.16	0.59±0.14
Porosity (%)	74.04±0.15	70.75±0.12	66.89±0.13
Compressibility index (%)	35.42±0.11	23.21±0.14	16.95±0.13
Hausner`s ratio	1.55±0.12	1.30±0.13	1.10±0.15
pH	6.05±0.01	5.07±0.02	5.26±0.01
Swelling capacity	3.50±0.15	2.93±0.12	3.25±0.4
Hydration capacity	3.50 ± 0.04	3.43 ± 0.12	2.38 ± 0.03
Compressibility	Very poorly compressible	Poorly compressible	Compressible

Figure 1: DSC thermograph for the natural powder of LTR

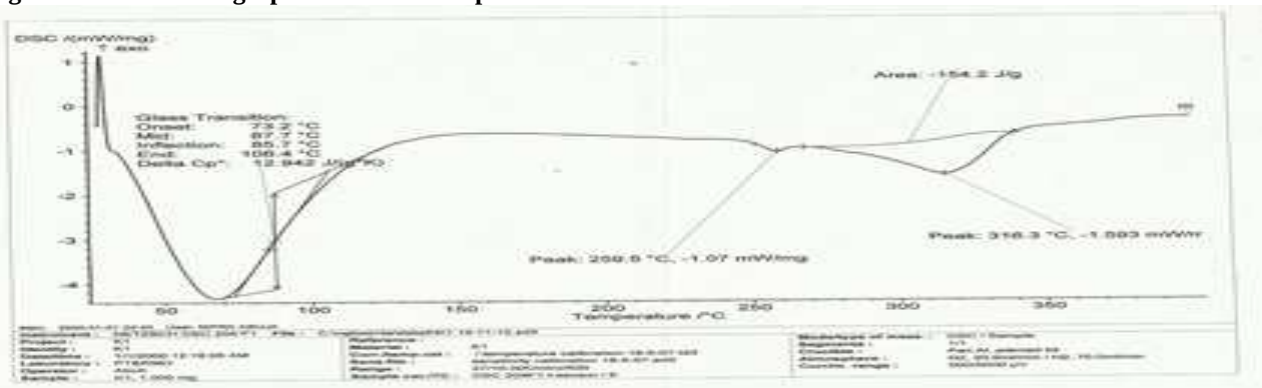


Figure 2: DSC thermograph for the processed powder of LTR

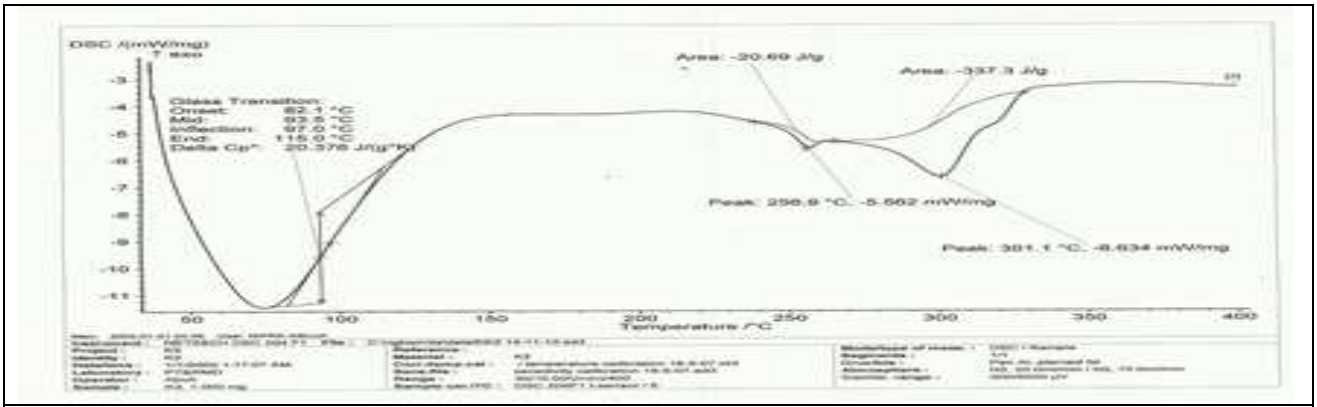
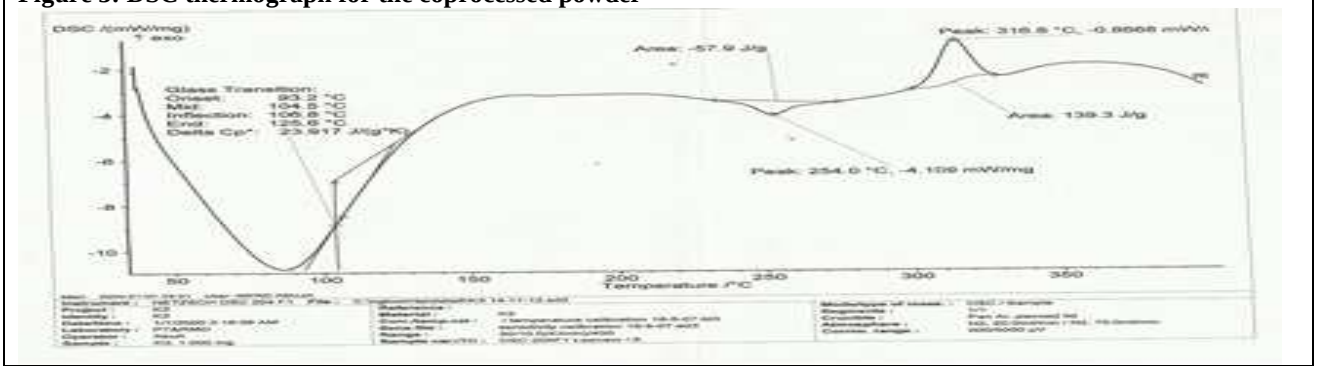


Figure 3: DSC thermograph for the coprocessed powder



CONCLUSION

The results obtained from this work show that the flowability and compressibility of *Lentinus tuber regium*powder was highly improved by coprocessing it with polyvinylpyrollidone. Considering this outcome as well as the swelling index, hydration capacity and its dilution potential for ascorbic acid andmetronidazole, itmay be useful as a directly compressible filler-binder and disintegrant in tablet formulations. It is suggested that this new powder be applied as directly compressible excipient in selected drugs, especially those with low dose. Its disintegrantbehaviour may also be investigated in several tablet formulations.

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