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Evaluation of rice husk as an excipient for the pharmaceutical industry

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Abstract
The pharmaceutical industry employs Aerosil 200V as an excipient in various formulations in a range of concentrations from 0.5 to 20%. The objective of the present work is to evaluate the behavior of silicon dioxide obtained from rice husk as a substitute for Aerosil 200V in the formulation of Valsartan 160 mg tablets. This new material was characterized and recognized its physical, mechanical and technological properties. Three pilot batches of tablets were manufactured and evaluated employing the rice husk ash and Aerosil 200V. Stability studies were done during six months including moisture influence during storage period. The rice husk ash meets established quality specifications in the pharmacopoeia USP and BP to colloidal silicon dioxide. At zero and six months the analyzed parameters were within the ranges established in the manufactured tablets with the two materials. It is possible to use silicon dioxide obtained from rice husk as an excipient in the Valsartan 160 mg tablets formulation as a substitute for Aerosil 200V and so decreasing agro-industrial waste.

Keywords: silicon dioxide, rice husk, excipient, Valsartan tablets

1. Introduction
The main component of the rice husk is silicon dioxide (SiO_2). This component is used for different purposes, such as the manufacture of photovoltaic cells, the synthesis of calcium silicates used in the production of sand-lime bricks in the cement industry, as filler material in paints and polymers industry and also to produce dielectric porcelain [1-4]. The methods for obtaining silicon dioxide from rice husk are widely known with a purity of more than 90 % and many authors have concluded that preliminary leaching of rice husks with acid or alkalis solutions boiled before thermal treatment with temperatures ranging from 500 to 1400 °C for various time intervals proved to be effective in substantially removing most of the metallic impurities and producing ash silica completely white [5-8].

In a recent study was obtained SiO_2 with over 99% of purity by washing the rice husk with a 1M hydrochloric acid solution and subsequently incineration at 700 °C for one hour following a dynamic method [9]. These parameters were obtained from a design of experiments 2^3 in which the rice husk was processed in different ways. The sample obtained was characterized by the pharmacopoeias BP2011 [10] and USP34 [11]. Also were analyzed by XRD, SEM and FTIR.

Colloidal silicon dioxide is used in the pharmaceutical industry to stabilize emulsions, as thixotropic agent, thickening and suspending gels, in the preparation of semi-solid, being used in concentrations ranging from 0.5 to 20%, generally [12]. In this work is presented the evaluation of the SiO_2 obtained from rice husk at pilot scale as substitute of Aerosil 200V, in the Valsartan 160 mg tablets formulation used in the diagnosis of arterial hypertension. The stability studies were carried out by two methods: from data obtained at the same temperature/conditions as those expected for the final product and from temperature-accelerated studies [13], determining quality-indicating parameters and the influence of moisture in the proposed packaging for tablets storage. No reports about use as excipient in the pharmaceutical industry.

2. Materials and methods

The SiO_2 was obtained from rice husk of national production (variety M-10). Aerosil 200V was obtained from Pharma, Germany. The reagents used in the analysis were all from Riedel-de Haën with the highest degree of purity.

Physical, mechanical and technological properties were determined and compared with those of Aerosil 200V. This excipient was added to the formulation as a lubricating agent in a proportion of 0.5%. Three pilot batches of Valsartan 160 mg tablets were prepared using the conventional wet method, with the help of a high speed mixer, determining the weight, height, hardness and friability at zero and six months.

Tablets were analyzed by the analytical technique for the quality control of Valsartan 160 mg tablets [14]. These requirements are description, identification, assay, dissolution and uniformity of dosage units. An analytical balance Mettler Toledo AB 204 and a drying oven Merck ULM-500 were used. The dissolution test was carried out in a dissolutor Erweka DT 600.

The concentration of the active ingredient in Valsartan 160 mg tablets was determined by High-Pressure Liquid Chromatography (HPLC) in a liquid chromatograph Shimadzu, model Prominence, Japan. The liquid chromatograph was equipped with a 235 nm detector and a 4 mm x 15.0 cm column that contains 5 µm packing RP-18. The flow rate is about 1.3 mL per minute. The mobile phase was a mixture of ammonium phosphate buffer pH 2.8 and acetonitrile (1:1 v/v) and the column temperature was 40°C. The injection volume was 20 µL.

The tablets stability was studied by shelf life and accelerated methods. For the shelf life the flasks were placed at room temperature (30 ± 2 °C) and 64% relative humidity protected from light and the accelerated stability was carried out by placing the samples at 40 ± 2 °C and 75% performing relative humidity. The description, identification, dissolution, uniformity of dosage units and assay test at zero, 1, 2, 3 and 6 months were measured. The tablets were packed in opaque white low density polyethylene bottles, screwed cap and tamper-resistant closure, performing a moisture influence study in order to measure the staunchness of the proposed bottle for tablets storage, placing in chambers to 84 % and 94 % of relative humidity to 30 ± 2 °C.

3. Results and discussion

The silicon dioxide obtained from rice husk presented similar characteristics to the Aerosil 200V (colloidal silicon dioxide). Its analytical quality was according with the requirements to the BP2011 and USP34 pharmacopoeias (11). In Table 1 are showed the physical, mechanical and technological properties of silicon dioxide obtained from rice husk ash and Aerosil 200V, existing difference in every analyzed parameter. The properties of silicon dioxide obtained from rice husk ash allow it can be used as an excipient in the tablets formulation as a lubricating agent, because it showed better results in flow properties and density than Aerosil 200V.

Table 1: Physical, mechanical and technological properties of rice husk ash and Aerosil 200V

Properties	Rice husk ash	Aerosil 200V
Poured bulk density (g/cm^3)	0.224	0.029-0.042
Bulk density of settlement (g/cm^3)	0.305	0.12
Flow rate (g/cm^2)	3.17 (Poor)	Very poor
Mean particle diameter	342 µm	7-16 nm

Three batches of Valsartan 160 mg tablets were prepared using the new material as a carrier instead of Aerosil 200V. The mass, hardness, height, friability and disintegration time were determined at zero and six months of manufactured as shown in Table 2. At zero and during of six months period the tablets were within the specifications.

Table 2: Technological properties of the tablets prepared using the new material.

Properties	**Limit**	**0 Month**	**6 Months**
Weight (mg)	576.0 ± 43.2	580.0	584.0
Height (mm)	5.2 ± 0.15	5.4	5.63
Hardness (Kgf)	7 ± 1	7,7	8
Friability (%)	≤ 1	0	0
Disintegration (minutes)	≤ 15	3	4

The tablets were characterized according to the quality specifications to Valsartan 160 mg tablets [14]. In table 3 were reported all the parameters analyzed complying with the acceptance limits. The tablets containing Aerosil 200V and rice husk ash showed similar bearings.

Table 3: Quality specifications at zero time of Valsartan 160 mg tablets prepared with rice husk ash and Aerosil 200V.

Test	Results		Acceptance Limits
	Rice husk ash	Aerosil 200V	
Description	Response	Response	White concave tablet beveled and lined
Identification	Response	Response	The retention times of the major peaks in the chromatogram of the Assay preparation correspond to those in the chromatogram of the Standard preparation, as obtained in the Assay.
Dissolution (%)	99.7	97.6	Not less than 75% (Q) of the labeled amounts of Valsartan is dissolved in 30 minutes.
Uniformity of dosage units (%)	98.8 CV=0.01	99.5 CV=1.27	85.0 – 115.0 % CV ≤ 6.0 %
Assay (%)	99.2 (158.7 mg/tab)	99.3 (158.9 mg/tab)	90.0 – 110.0 % (144.0 – 176.0 mg/tab)

The parameters analyzed (description and assay) during the term of six months in the shelf life and accelerated stability studies, are shown in Tables 4 and 5, respectively. At zero and during of six months period the tablets containing rice husk ash and Aerosil 200V meet with the chemical quality specifications, demonstrating that the product is stable at this time under the real storage conditions as it can be observed in Tables 2, 3, 4 and in Figure 1.

Table 4: Stability study by shelf life of three lots of tablets (30 ± 2°C and 64% relative humidity.

Test	Time (months)	Results	
		Rice husk ash	Aerosil 200V
Description	3 and 6	Response	Response
Assay (%)	3	99.2	96.8
	6	98.9	96.5

Table 5: Stability study by accelerated method of three lots of tablets (40 ± 2°C and 75 % relative humidity.

Test	Time (months)	Results	
		Rice husk ash	Aerosil 200V
Description	1	Response	Response
	2 to 6	No response	No response
Assay (%)	1	98.5	98.5
	2	97.7	97.8
	3	96.8	95.2
	6	95.1	94.9

In Figures 1 and 2 are shown the dissolved quantities in percentage during the term of six months in the different conditions of storage.

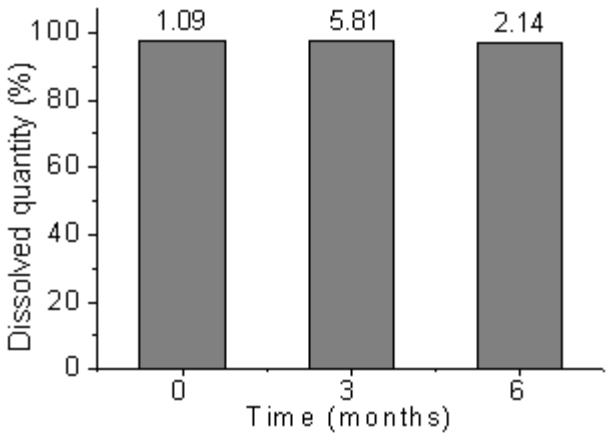

Figure 1: Valsartan dissolved quantities in the dissolution test in the shelf life stability study. The numbers above the bar indicate the standard deviation.

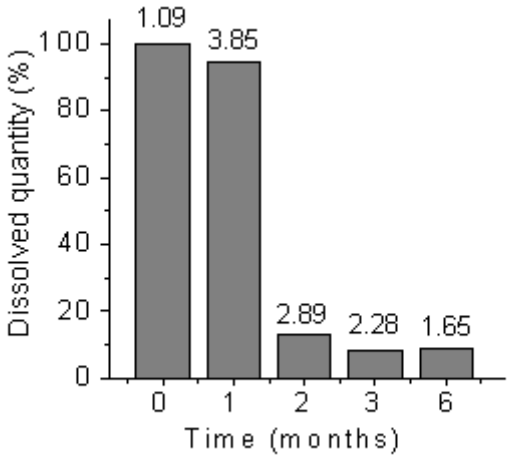

Figure 2: Valsartan dissolved quantities in the dissolution test in the accelerated stability study

In the accelerated study the experiment was affected in general, since the concentration of the active ingredient decreased by almost 5% over baseline. Similarly organoleptic changes were observed in the tablets because the cover was cracked and had an unpleasant odor as it can be observed in Table 5. In Figure 2 it can be appreciated that from the second month on the dissolution of the tablets was also affected, decreasing the study time (6 months) in more than 80%, so it may be thought that somehow these conditions disturbed the integrity of the tablet, possibly increasing its hardness and hampering the release of active ingredient. Valsartan is a highly hygroscopic active principle and it is probable that drastic employed conditions affected the physical stability of tablets. This comportment was similar in two formulations tablets.
The results of humidity study at three months of storage are shown in Table 6. No changes were done in parameters measure during 3 months of humidity study (84 and 98% relative humidity), so that the proposed packaging for storage is adequate.

Table 6: Results of humidity study in chamber at 84 and 84 % of relative humidity.

Test	Results			
	Rice husk ash		Aerosil 200V	
	84 %	98 %	84 %	98 %
Description	Response		Response	
Dissolution (%)	95.4	94.4	102.3	99.7
Assay (%)	99.8	99.7	96.5	95.0

Conclusions

Silicon dioxide was obtained, pharmaceutical grade, from an agroindustrial residue. From the technological and chemical points of view Aerosil 200V can be replaced by the Silicon Dioxide obtained from rice husk to use it as an excipient in Valsartan 160 mg tablets. The parameters analyzed in three batches don't differ at the beginning and in the shelf life stability during the term of 6 months.

Recommendations

It is recommended to send samples of the obtained product to other pharmaceutical companies to evaluate its behavior in other drug formulations.

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