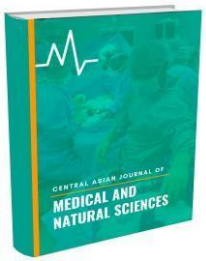

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Article

Research In The Field of Transferring The Technology of «ORTOF-S» Tablets Into Production

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Abstract: This study aims to transfer the technology for producing "Ortof-S" tablets, an innovative analgesic formulation, into industrial-scale production. Utilizing wet granulation within a high-shear mixer, the research investigates critical factors affecting granulation, such as mass, mixing time, and drying temperature, to optimize production parameters. Materials include diclofenac sodium, omeprazole, and various excipients. Laboratory testing established foundational parameters, while industrial tests examined granulation under scaled conditions to enhance bulk density, flowability, and moisture content. Key results demonstrate that higher mass and prolonged mixing significantly improve granulate quality, enabling consistent tablet strength and bioavailability. The study recommends specific granulation protocols for varying masses, providing a framework for scaling production while ensuring tablet efficacy. This research advances the pharmaceutical industry by establishing efficient methodologies for scaling up innovative solid dosage forms, supporting industrial implementation and alignment with GMP standards for quality control.

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1. Introduction

At the present stage of development of the pharmaceutical industry, research is being updated to optimize the development of effective innovative solid dosage forms [1, 4].

Pharmaceutical development of innovative solid dosage forms is a complex science–intensive process that, based on the biopharmaceutical concept, includes research on: in vitro model systems; disintegration test; dissolution test, tests of dynamics and kinetics of release of active substances pharmaceutical ingredients (API), comparative analysis of release, bioavailability, bioequivalence, correlation analysis of release kinetics in vitro and in vivo, as well as other technological, analytical and biopharmaceutical studies for the introduction of innovative pharmaceutical technologies into industrial production [2, 3, 6, 8].

Therapeutic efficacy and bioequivalent effect can only be determined through a comprehensive study of the influence of both pharmaceutical and biological variable factors, which in general can have a dominant influence at certain stages of the drug's life cycle, starting with industrial production and ending rational use, i.e. rational therapy and pharmaceutical care for the patient [4, 5, 7, 11].

Further pharmaceutical research on the introduction of innovative dosage forms requires the modernization of pharmaceutical production and the implementation of the concept of laboratory engineering. Efficient pharmaceutical production is facilitated by the optimization of technological processes, the integration of the domestic industrial industry and the strengthening of the positions of domestic manufacturers in the global pharmaceutical market, the introduction of GMP practices in industrial pharmaceutical production quality [7,8, 11].

The quality of the finished product significantly depends on the method of preparing the tablet mass for pressing [1, 2, 3].

The choice of preparation method for pressing, in turn, is determined by the characteristics of the initial powder components - pharmaceutical substances and excipients. First of all, these include the flowability and compressibility of the original powders [8, 10, 12].

The wet granulation method is the most widely used. In this case, binders introduced into the tablet mass make it possible to obtain tablets of sufficient strength. Disintegrants ensure rapid disintegration of tablets and high biological availability of the drug for the body. It should be noted that the widespread use of wet granulation in the production of tablets is explained not so much by the advantages of the method, but by the lack of the required technological properties of medicinal and auxiliary substances [2, 8, 12, 13].

The purpose of this study is to scale up the granulation process using the example of technology transfer in the production of recommended «Ortof-S» tablets using a wet granulation stage in a mixer-granulator with high shear force

2. Materials and Methods

Previously, laboratory studies studied the influence of pharmaceutical factors on the quality of the recommended «Ortof-S» tablets [2, 8, 10, 14].

At this stage of the study - the transfer of modern technology into production - we studied the granulation process conditions for the recommended tablets under production conditions. The pharmaceutical substance used was diclofenac sodium, omeprazole and excipients: lactose monohydrate, microcrystalline cellulose (MCC), potato starch, povidone (Plasdone™ K-29/32), calcium stearate.

The granulate under scaling conditions was obtained in a mixer-granulator, manufactured by ANCHOR MARK PVT, India. Volume 100 l. Productivity 60-70 kg/cycle, power consumption 2.2 kW. Loading manual, unloading is mechanical.

The research objects and auxiliary substances were mixed in a mixer - a planetary mixer, manufactured by Gaylord Pharma Sysrems, India. Number of rotations: conventional mixer from 12 to 24 rpm. Planetary mixer from 36 to 72 rpm, productivity – 100 - 140 kg/hour. Manual loading. Power consumption 10 hp, voltage 415 V, dimensions: diameter 700, height 800. For moistening, 5% potato starch paste was used. After humidification, it was carried out in a drying installation manufactured by ANCHOR MARK PVT, India. Model FBD-60, engine power 10 hp, heat 21600 kcal per hour, steam pressure 3 kg.cm3, steam quantity 50 kg/h, power supply - 380V, 50 Hz.

In all granulation processes, the influence of mixing time, mass of granulating mass, and drying temperature was studied.

In order to compare the economic efficiency of wet granulation and compaction methods, granulate of the same composition as that used by the compaction method,

weighing 20.5 kg, was prepared in the tablet workshop of «SAMO» LLC. The technological properties of the granulate were determined according to generally accepted methods.

A pre-weighed amount of active and auxiliary substances was loaded into the planetary mixer and the electric motor was turned on, causing the blade to rotate using the «Power» button of the magnetic starter. within 30-40 minutes. Then the rotation of the blades was stopped by pressing the corresponding magnetic starter button. Then the mass in the mixer was moistened with 5% potato starch paste. Moisten in small portions with rotating blades so that lumps do not form.

After moistening, the mass was mixed for 10-15 minutes until the moisture was evenly distributed, then the mass was transferred. The mixed, moistened mass was unloaded into a special collection trolley with a perforated bottom and transferred to the drying operation. The collection trolley was installed along the guides under the body of the drying unit and, using a hydraulic lift, was secured tightly to the flanges of the body. In this case, the collection trolley forms the bottom of the drying unit. The drying mode was set (air supply speed, drying temperature 40±5 ^{0}C, frequency of filter shaking, etc.).

Drying is carried out by hot, filtered air, which passes through the bottom of the collection trolley, bringing the dried material into a fluidized state, picks up moisture and is removed, passing through a fan, which is installed on the top of the unit. At the same time, carried away drug particles are retained on the filters.

We control the loading of wet mass, drying time, and drying quality. The dried mass must have a residual moisture content of up to 3.5%. We record the drying time. The dried mass was loaded into a mixer-granulator with high shear force for dusting through the loading hatch. The hatch was closed tightly. After the formation of granules, the electric motors were turned off. The dry granulate was loaded and a measured amount of potato starch and calcium stearate was added. The mixer lid was closed. By pressing the «Start» button, the electric motor was turned on, causing the mixer blades to rotate. Mixed for 10 minutes. Then the electric motor driving the blade rotation was stopped by pressing the «stop» button. The mixed mass must be homogeneous, the granules must be of the same shape (0.5-1.0 mm).

The above process was carried out every 5 minutes and the quality of the resulting granules was checked. When drying, the granulated mass was used and tested at different temperatures and drying times to determine the mode of preparation of granules under production conditions. In the next stage of the study, the following qualitative indicators of the resulting granules were studied, such as: appearance of granules, solubility, quantitative values of active substances, organoleptic properties and the amount of granules-anglomerates.

3. Results and Discussion

The results of studying the influence of the amount of mass and the duration of mixing the mass before granulation are given in Table 1.

As can be seen from Table 1, the mass and duration of mixing the mass before granulation has an intensive influence on the technological properties. Thus, with increasing mass and mixing time, there is an increase in bulk density (from 594.87 kg/m3 to 699.32 kg/m3) and angle of repose (from 36.38 degrees to 47.01 degrees). With increasing mass and mixing time, the indicators of flowability (from 6.0 10-3 kg/s to 4.83 10-3 kg/s) and residual moisture (from 3.51% to 1.97%) do not significantly decrease. The results of the study showed that the mass and drying temperature affect the technological properties of the studied mass. So, as in a small amount of granulated mass, the drying temperature also showed low data. In the case of a mass of 60 kg, drying time required an increase in temperature to 25-300C.

Thus, the mode of mixing the ingredients depends on the mass and time. When drawing up regulatory documents, it will be necessary to consider data on these two indicators separately.

Based on the data obtained, we suggest the following granulation mode for «Ortof-S» tablets: for a mass of 20 kg, the optimal time for mixing objects and excipients will be 5-10 minutes, for 40 kg of mass 20-30 minutes and for 60 kg of mass 30-40 minutes. In the next stage of the study, the influence of the amount of mass and the duration of mixing the mass after granulation was studied.

The results of studying the influence of the amount of mass and the duration of mixing the mass after granulation are given in Table 2.

The data obtained showed that the amount of mass and the duration of mixing the mass after granulation affect the technological properties of the granulated mass.

In studies devoted to the study of the influence of the temperature of drying mass (in different quantities), the research was carried out at temperatures of 5 – 100 C; 10 - 150 C; 20 -250 C and 25 - 300 C with subsequent study of the quality of technological parameters of the granulated mass.

Table 1

Results of studying the influence of the amount of mass and duration of mixing mass before granulation

Studied granule quality indicators	Weight, kg														
	20,0	40,0	60,0	20,0	40,0	60,0	20,0	40,0	60,0	20,0	40,0	60,0	20,0	40,0	60,0
	Duration of mixing the mass after granulation, min.														
	5 - 10			10 - 20			20 - 30			30 - 40			40 - 50		
Appearance	Granules of white or creamy color, homogeneous	-//-	-//-	-//-	-//-	-//-	-//-	-//-	-//-	-//-	-//-	-//-	-//-	-//-	-//-
Flowability, 10-3 kg/s	6,11	5,94	5,72	5,89	5,77	5,63	6,29	6,02	5,38	6,34	6,28	5,97	5,37	5,09	4,83
Angle of repose, degree	36,38	38,54	38,21	39,43	39,95	41,25	42,16	43,74	44,23	44,32	46,91	47,76	45,21	46,99	47,01
Bulk density, kg/m3	594,87	596,15	599,76	599,54	599,79	602,56	605,78	609,57	623,86	632,75	653,84	678,21	656,65	683,54	699,32
Residual humidity, %	3,51	3,51	3,44	3,22	3,35	3,18	3,09	3,61	3,67	3,31	3,45	3,33	2,27	2,14	1,97

Table 2
Results of studying the influence of the amount of mass and duration of mixing masses after granulation

Studied granule quality indicators	Weight, kg														
	20,0	40,0	60,0	20,0	40,0	60,0	20,0	40,0	60,0	20,0	40,0	60,0	20,0	40,0	60,0
	Duration of mixing the mass after granulation, min.														
	5 - 10			10 - 15			15 - 20			20 - 25			25 - 30		
Appearance	Granules of white or creamy color, homogeneous	-//-	-//-	-//-	-//-	-//-	-//-	-//-	-//-	-//-	-//-	-//-	-//-	-//-	-//-
Flowability, 10-3 kg/s	4,49	3,32	3,11	5,14	5,35	5,21	5,97	5,86	4,45	5,86	5,42	5,38	6,07	5,89	4,06
Angle of repose, degree	36,74	34,87	33,09	40,14	40,79	36,26	39,54	37,99	38,75	40,03	41,21	44,23	45,75	47,21	46,94
Bulk density, kg/m3	591,24	599,69	601,43	586,95	561,88	597,23	605,78	587,65	599,80	632,54	611,74	608,03	602,37	601,31	624,07
Residual humidity, %	4,58	3,94	3,98	3,18	3,25	3,22	3,09	3,48	3,98	3,17	3,28	3,33	3,11	3,12	3,35

Based on the data in Table 2 for a mass of 20 and 40 kg, the drying temperature after granulation was chosen to be 15 - 200C; a granulated mass weighing 60 kg under these conditions did not give positive results. Therefore, a drying temperature of 20 -250C was chosen for them.

Thus, for further research we used the above drying modes.

Further studies examined the effect of drying the granulated mass after granulation and the drying time of the tablet mass after granulation.

The influence of drying of the granulated mass after granulation and the drying time of the tablet mass after granulation was studied using the same masses (in different weights) that were prepared with the same objects and auxiliary substances.

The results of studying the effect of drying the granulated mass after granulation and the drying time of the tablet mass after granulation are given in Table 3.

As can be seen from Table 3, the weight and drying time of the tablet mass of the granulated mass after granulation and the tablet mass affects the properties of the mass.

In studies, to study the effect of drying time of the tablet mass after granulation, a time period of 10–20 and 30–40 minutes was used. Under these conditions, it was observed that the amount of granulated mass and the time of drying affect the technological properties.

Based on the data in Table 3, for a granulated mass weighing 20 kg, the duration time was chosen to be 10 – 20 minutes. The duration of drying of the granulated mass weighing 40 kg and 60 kg was chosen to be 30 - 40 minutes.

Also in the studies, the drying temperature of the tablet mass was studied (after powdering - before pressing). In these studies, the following picture was observed: for granulated mass, the amount of mass had no effect on drying. For all studied masses, we chose a temperature in the range of 40 - 500C.

Thus, for further research we chose the mode of drying the granulated mass after granulation and the drying time of the tablet mass after granulation.

Table 3

The results of the study of the effect of drying the granulated mass after granulation and the drying time of the tablet mass after granulation

Studied granule quality indicators	20,0	40,0	60,0	20,0	40,0	60,0	20,0	40,0	60,0	20,0	40,0	60,0
	Drying temperature of tablet mass, C^0						Drying time of the tablet mass after granulation, min					
	30 - 40			40 - 50			10 - 20			30 - 40		
Appearance	Granules of white or creamy color, homogeneous	-//-	-//-	-//-	-//-	-//-	-//-	-//-	-//-	-//-	-//-	-//-
Flowability, 10-3 kg/s	4,99	3,95	3,57	5,69	5,87	5,82	6,09	5,91	4,85	5,79	5,99	5,87
Angle of repose, degree	39,96	38,11	38,85	42,87	43,11	38,57	42,95	39,55	39,08	41,12	43,94	45,22
Bulk density, kg/m^3	584,38	579,93	599,78	577,99	559,82	583,61	589,53	568,35	589,43	611,27	587,35	598,24
Residual humidity, %	3,28	3,36	3,58	3,43	3,38	3,42	3,21	3,53	3,67	3,14	3,23	3,32

The next study was carried out on the granulated masses obtained by us using selected technological process modes, i.e., we studied the quality indicators of the resulting granulated masses.

The results of studying the quality indicators of the resulting granulated masses - ready-made granules - are given in Table 4.

Table 4

Results of studies of quality indicators of granulated masses (granules) «Ortof-S»

Appearance	Organoleptic properties	Solubility, %	Number of granules	Amount of active substance,%
Undefined shape, white granules with a specific odor	With a bitter taste	98,97	0,42	9,54

As can be seen from Table 4, the resulting tablets under the recommended technological process conditions make it possible to produce a high-quality finished product.

Thus, when scaling the granulation process, a risk analysis was carried out, the above factors influencing the technological process were determined and structured. It has been established that the most important stages are mixing and granulation itself.

4. Conclusion

In the studies, the drying temperature of the tablet mass was studied (after powdering - before pressing). In these studies, the following pattern was observed: for the granulated mass, the amount of mass had no effect on drying. For all studied macs, a temperature was selected in the range of 40 - 50^{0}C.

When scaling the granulation process, a risk analysis was carried out, the above factors affecting the technological process were identified and structured. It has been established that the most important stages are mixing and granulation itself.

As a result of scaling the granulation process, the parameters for carrying out wet granulation in a mixer-granulator were selected (optimal loading, rotation speed and drying temperature of the mass before and after granulation).

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