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It is our great pleasure to present this Supplement Issue on "*Macedonian Pharmaceutical Bulletin*" to the scientific and professional community. This supplement includes the short communications accepted for the *Seventh Congress of Pharmacy in North Macedonia with International participation 2022*, which was held in Ohrid, October 5-9, 2022.

The main theme of the Congress was "Modern trends in Pharmacy: opportunities and challenges" A broad spectrum of topics within the pharmaceutical sciences and practice carefully selected for this special occasion in order to build up a highly interesting and comprehensive program were covered. The contributions submitted to the Congress included 6 plenary lectures, 69 section lectures, and more that 200 posters. This Congress, followed the excellent international tradition, was attended by more than 1000 domestic and foreign participants. We received more than 287 short paper submissions from more than 15 countries. These numbers show that our Congress was aiming for the highest scientific standards, and that it can be considered a well-established venue for researchers in the broad fields of Pharmaceutical sciences and practice.

Sincere thanks to the hosts of the Seventh Congress of Pharmacy in North Macedonia with International participation, Macedonian Pharmaceutical Association and Faculty of Pharmacy, Ss Cyril and Methodius University in Skopje for their vision and commitments.

We would like to thank the companies that showed interest in supporting our efforts during the organization. We acknowledge the sponsoring companies: the platinum sponsor AD ALKALOID, Skopje, the golden sponsors: PLIVA-TEVA, EUROFARM, REPLEK and KRKA, the silver sponsor HEMOFARM and the bronze sponsors: GALENIKA, SEPTIMA and SALVEO,

We would also like to thank our members of the Scientific Committee for their volunteer time and dedication to the critical peer review process. We also wish to thank all the members of the Organizing Committee, whose work and commitment was invaluable.

On behalf of the Advisory and Scientific Committees, we would like to especially thank all internationally prominent researchers, whose work was supposed to be an essential part of the Congress. The interest in publishing their short communications in this issue of the Macedonian Pharmaceutical Bulletin is of a crucial importance for reinforcing the overall quality and standards of the bulletin. They give the state of the art of the recent advances in the field of pharmacy research.

The pharmaceutical sciences continue to grow as dynamic scientific interdisciplinary fields. We believe that published short communications will be an excellent source of scientific material in the fast evolving fields in Pharmaceutical sciences and practice.

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Your hosts
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This issue of *Macedonian Pharmaceutical Bulletin* contains short papers accepted by the Scientific Committee for the presentation at the 7th Congress of Pharmacy in Macedonia with international participation 2022.

The authors are fully responsible for the contents of their short papers.

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Short communication

Pharmaceutical and technological characteristics of barium sulphate tablets -the screening of various formulation factors

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Introduction

The study examined the development of barium sulphate tablets that do not dissolve in the digestive tract and are used as a contrasting agent for measuring transit time through the column. The main problem for obtaining non-degradable tablets is the formation of a compact polymer matrix that does not disintegrate in digestive fluids over a long period of time (Chaussade et al., 1986; Felder et al., 1984). In pharmaceutical technology, thermal techniques of granulation, extrusion, and the like, polymers and active pharmaceutical ingredients (APIs) are known for achieving better solubility of low soluble substances or for achieving slow release of highly soluble substances from solid preparations (Obradović et al., 2016)

Several different formulations were tested in which they were varied: the presence of different polymers Eudragit® RS PO and/or PMMA, wet granulation and direct compression procedure, different granulation of filler calcium hydrogen phosphate dihydrate, and the time of sintering in a pair of organic solvents of acetone or IPA at different time intervals. The results of the tensile strength of the tablets that are important for the further sintering process and the degradability of sintered tablets were monitored as the output parameter. In the final manufacturing process - tablet sintering, only formulations in which the tensile strength of the tablet was ≥20 MPa were used. For this reason, direct compression tablets, as well as wet granulation formulations with PMMA, are not sintered. The tensile strength of the tablet before and after sintering indicates that the "wet" granulation is more efficient with IPA because it produces better compacted granules (higher tensile strengths), while acetone is more efficient in the sintering process at 35°C , which is expected due to the higher vapor pressure at that temperature compared to the IPA.

Materials and Methods

The tablets are made by the wet granulation process, and the direct compression process, and the pharmaceutical and technological characteristics of the tablets have been compared. The API Barium sulphate (Merck, Germany) was used. The essence of the formulation is based on the use of two polymers: polymethyl methacrylate (PMMA DP 300 U) and copolymers of ammonium methacrylic acid (Eudragit® RS PO).The role of PMMA DP 300 U is to with Eudragit® RS PO synergistically form in physiological media an insoluble, completely impermeable and non-swelling martix regardless of the pH value of the media. Calcium hydrogen phosphate dihydrate, an insoluble excipient, was selected as the filler. Two types of this filler were selected, powder and fine granular (Emcompress®) intended for direct compression due to improved flowing and compressible properties. Magnesium stearate was used in order to achieve adequate lubrication and to eject the tablets from the matrix. Acetone and/or IPA were chosen as solvents in combination with concentrated ethanol and water.

Wet granulation

In laboratory tests, mixing and wet granulation were carried out in a high shear mixer and dried at 50 °C in a fluidization oven. A vacuum processor was used for the pilot test. In the vacuum processor homogeneous mixing of the previously measured barium sulphate, calcium

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hydrogen phosphate dihydrate, Eudragit RS PO, and PMMA DP 300 U. The granulation solution is a mixture of acetone or isopropanol, concentrated ethanol, and purified water, i.e. isopropanol and purified water and purified water. The wet agglomerated mass is dried in a vacuum processor by heating to a temperature of 50 °C., and the vacuum is included with occasional stirring until is achieved loss on drying of not more than 1% (at 105 ^{o}C). Magnesium stearate was added to the diluted granulate and further stirred.

Tableting

Compression of laboratory trials was performed on an eccentric tablet press EKO type, and pilot trials were performed on a Kilian rotary tablet press Synthesis 500. For the 80 mg dose, the characteristics of the tablets were: mass: 0.268 g, diameter: 8.8 - 9.2 mm, and hardness: at least 20.0 MPa.

Sintering

Tablets were sintered in a sealed chamber saturated with either acetone vapor or isopropanol vapor at 35ºC (± 2 ºC) for 8h, 16h, 24h, 32h, and 40h.

Drying

After sintering, the tablets were dried or residual acetone or isopropanol is removed to a maximum of 2.5 mg/tablet. The sintered tablets were dried according to the scheme: 1) Temperatures 22 ºC for 16 h, 2) 40ºC for 24 h, 3) 50 ºC for 8 h and 4) 55ºC for 8 h.

Results and discussion

In the case of tablets made by direct compression, it was not possible to achieve the corresponding mechanical characteristics of the tablets: the strength and friability, which were necessary for the further process and manipulation, or consolidation, by sintering in an organic solvent vapor. Formulation made with PMMA DP 300 U, without the addition of the Eudragit® RS PO polymer, could not be compressed due to the spherical shape of PMMA DP 300 U which is extremely unfavorable for compression. The results of tablet tensile strengths before and after sintering indicate, for IPA and acetone solvents, that IPA solvent is more effective for wet granulation because it produces better compacting granules (higher tensile strengths are obtained), while acetone is in the sintering process at 35 °C a more efficient solvent, as expected given the higher vapor pressure at that temperature compared to IPA. The time interval during which the disintegration was tested was up to 7 days because it is the interval during which the transit of the tablet through the column in subjects with slow passage is examined *in vivo*. When it comes to the efficiency of the organic solvent in the process of polymer matrix consolidation by sintering, the slightly lower efficiency of isopropanol compared to acetone is observed. The sintering time has a significantly greater effect on matrix consolidation. The criteria for intact barium sulphate tablets within a 7-day time interval was fulfilled only by formulations with a mixture of Eudragit® RS PO and PMMA DP 300 U polymers obtained by granulation with acetone or isopropanol using a sintered process during 35h.

Conclusion

Tests of various formulations and technological parameters in the production process have shown that in order to obtain a contrast agent for testing the functional radiology of the colon, rectum and anal canal, i.e. measuring the transit time through the colon, which meets the defined criteria, optimal formulation is with calcium hydrogen phosphate dihydrate powder, an equivalent amount of Eudragit RS PO and PMMA DP 300 U polymers, isopropanol as solvent in addition to ethanol and water in the process of wet granulation, and sintering process in an organic acetone solvent vapor at 35°C.

References

Felder, E., Zingales, M., Jellicich, M., 1984. Process for the preparation of barium sulfate of increased flowability and density, suitable as a radio-opaque component in radiographic contrast agents, product obtained according to this process and the radiographic contrast agent produced therefrom Patent US 4,588,574.

Chaussade, S., Roche, H., Khyari A., Coutourier, D., Guerre, J., 1986. Measure du temps de transit colique (TTC): description et validation d une nouvelle technique. Gastroenterol Clin. Biol. 10, 385-389.

Obradović, N., Filipović, S., Đorđević, N., Kosanović, D., Pavlović, V., Olćan, D., Đorđević, A., Kachlik, M., Maca K., 2016. Microstructural and electrical properties of cordierite-based ceramics obtained after two-step sintering Technique, Sci. Sinter. 48, 157-165. https://doi.org/10.2298/SOS1602157O