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Development of modified release solid dosage forms based on hot-melt technologies

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1. Introduction and aims:

Oral formulas are the most widely used and marketed among the other common drug delivery systems. Patient compliance and non-invasive administration make them perfect targets for the continuous development and investment. Market researches forecast the growth of global oral solid dosage pharmaceutical formulation market from US$ 493.2 Bn in 2017 to US$ 926.3 Bn by the end of 2027.

The mostly widespread drug delivery systems are the matrix formulations. The earliest publication with the title containing tablet matrix is from 1958. These platforms are able to regulate drug dissolution from the formulation in a controlled manner. The matrix contains special or exclusive excipient or excipients which are capable to alter or to control the drug release rate.

From technological aspect, to create matrix systems several methods are available. Direct compression of powder blend to create monolithic platforms is the simplest way to integrate APIs into matrix systems. Nevertheless, poor flowability and compressibility of the powder blend can be a crucial problem. Another possible method is the extrusion processes. During extrusion the homogenous blend of the API and the excipients is pushed through a die under high pressure. Matrix systems can be formulated into capsule forms as well. Encapsulation needs no compressional step, additionally, instant taste masking is achieved. Traditionally, hard capsules are filled with solid matter (powder blend, granules, pellets). The softgels are one-piece closed shells in which the filling is a liquid or semi-solid non-aqueous solution or suspension. However, this basic difference between the state-of matter of the fillings are not so characteristic to the two types of the capsules.

With the possibility of filling non-aqueous solvents and other liquid or semi-solid excipients (surface active agents, co-solvents) into the capsule shells, the bioavailability of poorly water-soluble drugs can be increased. A simple way is to dissolve the API in lipid based carrier, which can be absorbed on the lymphatic route, similar to the absorption of the fats. Solid dispersions are favoured to increase the bioavailability of the API for several reasons. The release of the API is independent of the pH of the dissolution media, ease of manufacture with low cost and several excipients are available. On the other hand, further excipients can be used to formulate self-emulsifying systems too, capable to disperse the API in the forms of micron- or nanosized droplets in the digestive juices. The Lipid based Drug Delivery Systems could not only increase the bioavailability due to increased solubility. The sustained release of the APIs is also possible. Based on the applied excipients, inert matrix systems can be formulated Furthermore, water soluble or swellable and mouldable excipients may be used to create erodible matrices.

The dissolution of the API is vital biopharmaceutic property, since the dissolved drug can be absorbed. Beside this, the human digestive tract shows segmental differences in its ability to absorb drugs. It is well known that some API possess site specific absorption, in other words these drugs have narrow absorption window. In these

cases, it is advantages to release the drug in a sustained manner in the upper GI tract. Gastric retention devices or delivery systems could provide a solution for this problem.

Conventional forms, such as tablets or capsules, but floating multiple unit systems and semi-solid or *in situ* gel forming formulations are used in the practice. One of the simplest way is to compress a mucoadhesive polymer API blend into a matrix tablet. In this case the polymer is responsible for the adhesion and the sustained release of the API, as well. Mucoadhesive systems adhere to the mucin layer covering the stomach wall, which is advantageous in term of the absorption of the drug thanks to the proximity of the mucosa and the dosage form. The disadvantage of the mucoadhesive formulations is that they are in contact with the mucus layer, however the layer in unstationery and shows certain turnover. Unfolding or expandable formulation are filled in their compact form mostly into hard capsules. After swallowing and disintegration of the capsule, the formulation unfolds or expands to multiple volume regarding its compact size due to certain changes. It is elementary to use such excipients which are biodegradable in the stomach to prevent accumulation of the empty carriers.

We aimed to design and formulate a modified release HGC system, based on a new formulation method with *in situ* lipid matrix formation. We fully characterized not only the properties of the formed lipid matrix, but we tested also the effect of heating on HGCs.

Our second aim was to design, build and use a batch type in-house apparatus to produce lipid based monolithic matrices. We created low density, sustained release formulations with instant floating properties in acidic buffer without the need of gas generation and entrapment. After foaming the formulation can be easily filled into the final dosage form, hard-gel capsules and then the foam quickly solidifies upon cooling keeps its structure resulting the floating properties.

2. Materials and methods:

2.1. Materials:

For the development of the MR capsules, based on *in situ* matrix formation, we used Gelucire 50/13 (GC) was kindly gifted from Gattefossé (Saint-Priest, France), cetostearyl alcohol (CSA), acetaminophen (ACP) and metronidazole (MNZ) were Ph. Eur. grade and purchased from Hungaropharma (Budapest, Hungary). Microcrystalline celluloses (MCC), Vivapur 200, 12 and 100 were gifts from JRS Pharma (Rosenberg, Germany). Diclofenac sodium (DS) was purchased from Cayman Chemical Company (Ann Arbor, Michigan, USA). Ethylcellulose (EC), Ethocel™ 100 FP Premium was a kind gift from Colorcon Limited Budapest (Budapest, Hungary). HGCs (Coni-Snap®, size 0) were purchased from Capsugel (Morristown, New Jersey, USA). Other reagents were all of analytical grade and purchased from Sigma-Aldrich Kft. (Budapest, Hungary).

For the experiments of the foamed, gastroretentive solid dosage forms Polyethylene glycol 4000 (PEG4000), stearic acid, type 50 (SA) and metronidazole (MNZ) were Ph. Eur. grade and purchased from Molar Chemicals Ltd. (Halásztelek, Hungary). Labrasol® was kindly gifted from Gattefossé (SaintPriest, France). Other reagents were all of analytical grade and purchased from Sigma Aldrich Kft. (Budapest, Hungary)

2.2. Experimental methods of the *in situ* lipid matrix formation in MR capsules:

2.2.1. Capsule tests:

It is well known that water content is crucial for maintaining the mechanical properties of gelatine and it has been shown that the structural and mechanical properties of hard gelatine capsules are a function of relative humidity. Empty HGC shells were divided into two groups, covered and uncovered. Covered were filled into a glass container with a fixed plastic cap, uncovered were poured into disposable plastic weighing boats. Then, they were placed into the preheated hot-air oven (Memmert SFE 550, Memmert GmbH, Germany) for 10, 20, 30 minutes at 63 °C (19). Capsules were weighed and loss of drying was calculated before and instantly after, heating. The changes in the moisture content were also investigated 1 day, 1 week and 1 month after the experiments. For the loss of drying test HGCs were dried overnight in an oven at 105 °C (18).

Two different types of experiments were carried out. Firstly, we did the Tube-test, which consists of a 100 g weight dropping on an empty capsule from a height of 8cm (18). The weight was a stainless steel weight with a diameter of 245mm. 150 empty capsules were investigated in three groups, uncovered capsule were placed in a glass baker, covered capsule were placed in a glass baker sealed with aluminium foil and control group. All capsules were heated in oven for 11 mins at 63 °C except the

control. After heating, capsules were allowed to cool down and Tube test was carried out. In the second experiment 20 empty shells and 20 shells filled with lactose were heated as described above. After cooling both groups were tested for cracks and leakage in a friability tester (Erweka TA40). Rotation speed was 25 rpm. Tests lasted for 4 and 12 mins. Capsules were individually visually checked for any crack and powder leakage.

2.2.2. Selection of the appropriate adsorbent.

We tested the effect of different types of cellulose derivatives as absorbents on the texture of matrices with the following method. GC, CSA and the cellulose, either EC or different grades of MCC, were homogenized in mortar with a pestle and the blend was filled in the cavities of a PVC/PE/PvdC blister (diameter: 11 mm, depth: 8 mm). The blends contained 15% CSA, 40% GC and 45% cellulose derivatives. Then the blister was placed into a preheated oven (Memmert SFE 550, Memmert GmbH, Germany) for 11 minutes at 63 °C. The formed matrices were extracted after cooling, observed visually and their crushing strength was measured with a CT3 texture analyser with a maximum load of 4500 g (Brookfield Engineering Laboratories, MA, USA) Texture Pro CT program was used for the measurements (Brookfield Engineering Laboratories, MA, USA). The amount of the absorbent was experimentally determined for each API.

2.2.3. Preparation of the Sustained Release Capsules:

6.5 g of each composition were homogenized in a mortar, each empty capsule shells were filled by a manual capsule filling device. After filling they were heated in the oven for 11 minutes at 63 °C. The capsules lied in a horizontal position in disposable plastic weighing boats. After the melting procedure the capsules were slowly cooled to 35 °C in 5 minutes by letting cool air inside. Finally, the capsules were allowed to cool to room temperature.

2.2.4. Mechanical Tests of the SR Capsules:

To evaluate the brittleness of the formed matrices 3 point bend test was chosen. A custom made adjustable fixture was designed and made for the test. The measurements were made with the CT3 texture analyser with a TA7 knife edge probe, the maximum forces to break the blocks in halves was recorded with the Texture Pro CT program. The effect of ageing was also investigated by storing the samples for a month. Samples were stored in air-tight glass containers between 18 °C and 25 °C and at 40%-65% relative humidity.

To investigate the significant softening found in DS formulations (DS1), plasticity tests was performed with the matrices. The texture analyser was equipped with an acrylic cylinder, TA11/1000, (d: 25.4 mm) and the device was programmed to compress the blocks with a constant speed (0.50 mm/s) until a 4500g of resistance is detected, while the programme recorded the distance.

2.2.5. NIR Measurements:

A ThermoScientific Antaris II FT-NIR spectrometer (ThermoFisher Scientific, USA) with an integrating sphere accessory with internal background was used for the spectroscopical investigation of the samples. The resolution was set to 4 cm-1, the scan number was 128 and H2O and CO2 corrections were applied. The spectra were evaluated with the use of Spectragryph optical spectroscopy software v1.0.2 (Dr. F. Menges, Berchtesgaden, Germany).

2.2.6. Thermal Analysis:

Differential scanning calorimetry (DSC) measurements were performed with a DSC 821e (Mettler-Toledo GmbH, Switzerland) instrument. During the DSC measurements the start temperature was 25 °C, the end temperature was 500 °C and the applied heating rate was 10 °C min-1. The measurements were performed in an Ar atmosphere (purity = 99.999%, 70 cm3 min−1 flow rate). 5±1 mg sample was measured into an aluminium pan (40 µl). The curves were calculated and were evaluated with STARe Software.The thermal characteristics of the sample mass loss were determined with a thermal gravimetric analyzer TG/DSC1 (Mettler-Toledo GmbH, Switzerland) operated under N_2 atmosphere (purity = 99.999%, 70 cm3 min−1 flow rate). During the TG measurements the start temperature was 25 °C, the end temperature was 500 °C and the applied heating rate was 10 °C min-1. 10±1 mg sample was measured into an aluminium pan (100 µl). The curves of DSC and TG results were calculated and were evaluated with STARe Software.

2.2.7. Powder X-Ray Diffraction Study:

For the XRPD measurement the samples were finely powdered. The powder was mixed with minimum amount of CryoOil (Mitegen) and a small ball was formed and fixed on a Mylar loop. The X-ray measurement was performed at 298(2) K on a Bruker D8 Venture diffractometer with Photon 200 CMOS detector, equipped with a multilayer mirror monochromator and a CuKα INCOATEC IµS micro-focus source (λ=1.54178 Å). Phis scans for 360° were collected and the optimized detector distance was 120 mm and data collection time was 60 s. The raw frame data were collected and frames were integrated using the Bruker APEX3 program (v2017.3 *Bruker AXS Inc.).

2.2.8. HPLC Analysis of the DS Capsules:

Due to the detected interactions between the DS and the melt, HPLC analysis was performed to detect any degradation product beside pure DS. The HPLC system Merck-Hitachi ELITE LaCrom consisted of a pump (L-2130), degasser, automated injector, column oven (L-2300) and a photodiode array detector (DAD). The column module was kept at 25 °C, the DAD was set to collect signals within the spectral range of 220-400 nm. The separation of dissolved components DS capsules and the pure API was performed on the Zorbax Eclipse Plus C8, (4.6 x 150mm, 5.0 µm, end-capped) (Agilent, Santa Clara, CA, USA). The injected volume of samples was 20 µl. A flow rate of 1.0 ml min-1 was applied. The mobile phase A was an aqueous solution

containing 0.5 g/L of phosphoric acid R and 0.8 g/L of sodium dihydrogen phosphate R, adjusted to pH 2.5. Mobile phase B was methanol. The two phases were mixed in a ratio of 34:66 (v/v). The analyses were performed with EZChrome Elith™ software (Hitachi, Tokyo, Japan) for collecting and processing data. Fresh samples were compared to stored samples, in this case, the storage time was 2 years, with the same storage conditions as mentioned in 2.6.1. To analyse or detect any degradation product beside pure DS, samples were dissolved in 900ml of phosphate-buffer solution (pH 6.8) and after filtration (0.2 µm PES membrane filter) were further diluted 10 or 100 times with methanol. This solution was injected.

2.2.9. In vitro Drug Dissolution:

Rotating basket method was used for dissolution tests, using Erweka DT800 dissolution tester. The rotation speed was 100 rpm, the dissolution medium was simulated intestinal fluid (SIF) prepared according to the European Pharmacopoeia without pancreatin and the temperature was maintained at 37 ± 0.5°C. As a sample, 4 millilitres of the dissolution medium was withdrawn at predetermined intervals and the volume of the dissolution medium was kept at 900 mL by adding fresh medium. Samples were filtered with a 0.45 µm PTFE membrane filter and 0.5 ml of the samples were diluted by adding 4.5 ml of purified water (PW). The released amount of the DS, the ACP and the MNZ was measured spectrophotometrically (Shimadzu UV-1601, Shimadzu Corp., Kyoto, Japan) at 276 (23) 243 (24) and 320 (25) nm, respectively. Three samples from every composition were tested. Freshly prepared samples and capsules after 1-month storage were also compared.

2.2.10. Mathematical Analysis of the Drug Release Profiles:

To determine the similarity or difference between the drug release profiles of the matrices, a model independent approach, similarity, f2 and difference, f1 factor was calculated for each composition after formulation and after 1 month of storage. Dissolution efficacy (27) was also calculated after formulation and after 1 month of storage. To determine the drug release kinetics of APIs from every composition, release data was fitted to zero order, first order and Korsmeyer-Peppas model using SigmaPlot (Systat Software Inc., USA) (27).

2.3. Experimental methods of floating moulded dosage form by melt foaming

2.3.1. Foaming device setup:

In-house apparatus was designed and built from polypropylene tube. The equipment is presented in Figure 1. Briefly, the apparatus is a cylinder with the volume of 60 mL, which ends at the bottom in a 10 mm wide valve. The outer surface on the sides and at the bottom are water-jacketed with 6 mm plastic tubing. The jacket is connected to a Julabo F25 temperature control unit equipped with a Julabo ME

circulator. The agitator is made of 1 mm wide stainless steel wires. The agitator is connected to an IKA EURO-ST D overhead stirrer.

2.3.2. Effect of temperature on the viscosity of the molten suspension:

The apparent viscosity of the molten PEG4000 containing 30 m/m% MNZ was measured by a Rheolab QC rheometer (Anton Paar Hungary Ltd.) equipped with a concentric cylinder jacketed measuring cell. The cell was connected to a Viscoterm VT 2 waterbath (Anton Paar Hungary Ltd.). The viscosity curves were recorded with the RheoPlus software. The measurement cell was heated to 65 °C prior to loading with the molten and homogenous MNZ suspension. Viscosities were measured between 65 °C and 53 °C with the difference of 2 °C with constant shear rate of 1000 rpm. The maximum viscosity values were plotted as a function of temperature.

2.3.3. Preparation of solid foams:

Forty grams of the different compositions (M1-M7), presented in Table 1., were foamed by the following method. PEG 4000, Labrasol® and SA was measured and loaded into the preheated foaming equipment with the slow agitation of 50 rpm at 65°C (jacket temperature). After complete melting, MNZ (average particle diameter: 180-125 microns) was dispersed for 10 min in the molten mixture, at 300 rpm. Cooling was started by setting the temperature of the water circulating in the jacket to 53 °C. After 5 min when the temperature of the water reached 53 °C foaming was done by heavy agitation at 2000 rpm and dispersing air into the molten mass. The procedure was done for 5 min maximum. For further investigations of the foamed matrix system, the foamed and hot dispersion was moulded into a steel mould (V= 1.027 mL, bullet shape) and cooled.

2.3.4. SEM analysis and diameter determination of foam cavities:

Hitachi Tabletop microscope (TM3030 Plus) was used to characterize the solid foams. Samples were split in halves and were attached to a fixture with a double-sided adhesive tape containing graphite. Average diameter of the voids were calculated by measuring the diameter of hundred random cavities (GIMP 2.8 software) from at least 3 regions of the solid block.

2.3.5. Microtomography

In order to characterize and visualise the internal microstructure of solidified molten foamed and unfoamed dispersion of M7 samples, the following protocol was developed. The foaming process, described above was done. A small portion of the homogenous dispersion was removed prior to the foaming step, from the jacketed vessel with a PET tube (internal diameter: 5.0 mm) attached to a 10 mL syringe, to obtain the unfoamed sample. After the foaming step another portion was quickly and carefully removed from the vessel with a similar PET tube to prepare the foamed sample. The molten dispersions were allowed to cool down and solidify in the plastic tubes. After solidification the rods of the solid samples were cutted into 5-6 mm long cylinders. A

random foamed and unfoamed cylinder was attached to each other with a soft glue and this preparation was scanned later. A SkyScan 1272 compact desktop micro-CT system was used for the measurement. Scanning parameters were the following: image pixel size: 5 microns, matrix size: 1344x2016 (rows x columns), Source Voltage= 50 kV; Source Current= 200 μA, Flat Field Correction and Geometrical Correction were used. After scanning SkyScan NRecon package (Version: 2.0.4.2) was used to reconstruct cross-section images from tomography projection images. Post-alignment, Beam-hardening correction, Ring artefact correction and Smoothing were done. The output formats were DICOM and BPM images.

2.3.6. Dissolution and floating test

900 mL of hydrochloric acid media, pH: 1.2 without pepsin was selected for dissolution tests and prepared according to the European Pharmacopoeia. Rotating paddle method with the rotation speed of 75 rpm and 37 °C was set up in a dissolution tester (Erweka DT 800). Samples of 4 mL were withdrawn after 5 min, 15 min, 30 min, 1, 2, 3, 4, 5, 6, 7, 8 and 10 hours. The samples were diluted with purified water and filtered through a 0.22 μm PES membrane syringe filter. The released amount of MNZ was determined by UV/VIS spectrophotometer (Shimadzu UV 1601, Shimadzu Corp. Kyoto, Japan) at 278 nm. Three random samples were selected for the tests from every composition. Floatation was inspected at the beginning, during and at the end of the test also.

2.3.7. Water uptake and matrix erosion studies

Erosion and swelling properties of the solid formulations were determined by the following method. The initial weights of the samples were recorded before the experiment, then they were placed into the dissolution vessels as described in section Dissolution and floating test. After 1, 3, 5, 7 and 10 hours samples were carefully removed with a plastic net and the weight of the wet samples were measured after blotting the excess water. The samples were then dried in an oven (Memmert SFE 550, Memmert GmbH, Germany) at 45 °C for 48 h, after cooling to room temperature their constant weight was measured. Three samples were tested from all compositions. Water uptake % and remaining masses of the foams were calculated

2.3.8. Mathematical analysis of the drug release profiles

The model dependent and independent analysis of the release profiles of M4-M7 compositions were done according to Section 2.2.10. However in these cases, only the fresh samples were analysed and compared.

2.3.9. Dissolution coupled texture analysis

Texture analysis was chosen to characterize the mechanical properties and structure of the dry and wetted foamed compositions. Dry samples were tested at 25 °C without immersing them into acidic dissolution media. To monitor and determine hardness changes and erosion of the floating formulations, three random samples were

placed onto dissolution vessels containing 900 mL of 37 °C pH 1.2 hydrochloric acid media with 75 rpm paddle speed. To visualise water permeation into the matrix the media was coloured with 20 drops of 5 m/m% Sicovit® Tartrazine (BASF) solution. The samples were carefully removed after 1, 3, 5, 7 and 10 hours later and excess water was removed by using soft and plastic net and tissues. Wet and dry samples were analysed by the following method. Brookfield CT3 texture analyser was equipped with an acrylic cylinder, TA25/1000, (d: 50.8 mm) and the device was programmed to compress the blocks with constant speed (0.50 mm/s) until 4500 gram of load. At the target pressure the device fixed the probe for 5 seconds as a hold time. Following the hold time, the probe returned to its initial position, thus the measurement took 20 seconds per sample. The load values were plotted in the function of time (s) to present the changes in the texture in real-time.

2.3.10. Statistical analysis

For statistical analysis SigmaStat software (version 3.1, SPSS Inc.) or GraphPad Prism® (Version 6.01, GraphPad Software Inc.) was used. Unpaired t tests were performed when two groups were compared, one-way ANOVA was chosen when comparison of multiple groups were performed in the caes of the *in situ* lipid matrices or the floating moulded dosage forms. Differences were considered significant at $p < 0.05$.

3. Results:

3.1. Experimental result of the *in situ* lipid matrix formation in MR capsules

3.1.1. Effect of heating conditions on the empty capsules:

Control capsules had 14.1% moisture content which was due to its appropriate storing, in accordance with the supplier's recommendation. By preventing the unwanted water loss, covered capsules still had a 12.97% loss of drying even after 30 minutes of heating. Without any preventive measures, even 10 minutes of heating resulted a drop to a LOD value of 9.38%. After 20 and 30 minutes the uncovered capsules retained only 7.63% and 7.22% of their moisture. As a result of the Tube test, 16 uncovered capsules broke compared to the 4 covered broken shells, control capsules were also examined, only three capsules cracked from the fifty. In the modified friability test no cracks and no powder leakage was found in the case of empty and the lactose filled shells even after 12 mins.

3.1.2. Selection of the appropriate adsorbent

Due to their extreme brittleness, matrices with Vivapur 200 and 12 cracked and fall apart even though the careful removal from the PVC blisters. Vivapur 101 and Ethocel Std. 100 hold the structure together. Their crushing strength was 194.5±55.3 and 348.38±40.61 grams respectively. Since microcrystalline cellulose has disintegrant properties (30) and Ethocel Std 100 provided the strongest block, for the further experiments Ethocel Std 100 was used as adsorbent.

3.1.3. Mechanical tets of the SR capsules

All of these compositions had an average mechanical resistance greater than 571.3 gram. The results, the performed t-test and ANOVA showed that short time storage had no significant effect comparing the ACP formulations ($p>0.05$). Investigating the hardness changes upon storage in the cases of the MNZ formulations showed intermediate values comparing the ACP and the DS formulations and the 1-month storage caused no significant changes ($p>0.05$). Unlike the others, DS formulations, namely DS1 became significantly softer than the DS2 and DS3 after one month of storage ($p=0.021$). Similar phenomenon was also observed when fresh and stored DS1 was compared ($p=0.023$). To investigate the significant softening found in DS formulations (DS1) plasticity tests was performed with the matrices. Test results are presented in Table III. Interestingly, the softening was not significant in the case of DS1 ($p>0.05$), but the hardening of the DS2 and DS3 compositions were found to be significant before and after test ($p=0.0236$; and $p=0.0052$).

3.1.4. NIR measurements:

The NIR spectra of the DS compositions present peaks at 4328 1/cm as a result of the overlap of the characteristic signals of GC, EC and CSA. Slight shift can be observed toward lower wavenumbers in the cases of the theoretical spectra as the ratio of the CSA in the matrix increases. These alterations however appear less intensively with the fresh matrices. all relative peak intensities decrease, signal shifts and widening to higher wavenumbers can be seen as a comparison to the peak at 4252 1/cm. A possible explanation is that an interaction could be between EC and GC, DS might be involved also. Diclofenac also has characteristic peaks at 4798, 4842, 4856 and 4894 1/cm. The relative intensity of the first peak is higher compared to the fourth peak, but during storage the difference between the two peaks disappeared. The peak's relative intensity at 4893 1/cm increases in all DS samples, the ratio of intensity sets back as seen at the pure API.

Similar events were recorded with ACP samples.28 1/cm. CSA also shifts the peak toward 4322 1/cm. In the region of 4550-5000 1/cm ACP has many characteristic signals (4647, 4719, 4895, 4945 1/cm). The wavenumbers and the relative intensities are constants. The double peaks at 5665 and 5771 1/cm are also present, but during storage peak changes were only detected at 5771 1/cm, peak broadening and decrease in the relative intensity.

In the case on MNZ containing samples the same overlapping of characteristic peaks of GC, EC and CSA may be observed, but similarly to the ACP containing samples the characteristic peaks of MNZ at 5862, 5896, 5932, 6009 and 6061 1/cm remained unchanged both in powder and melted form, and during storage, indicating that there is no interaction between the API and excipients.:

3.1.5. Thermal analysis

The thermal gravimetric analysis proved that all of the APIs and the excipients are stable at the temperature of the experiment, no sign of chemical decompositions or changes were detected under 100 °C. The dissolved material decomposed at 233.65°C, 228.41°C and 233.43°C for DS1, DS2 and DS3 and this phenomenon occurred at the stored samples. Compared to its original temperature of decomposition (290.68 °C) this is a significant change. Based on the TG curve of the pure DS, it is very likely that its melting is associated with thermal decomposition. The DSC curves of the GC and CSA shows wide endothermic peaks at 52.27 °C and at 56.27 °C, respectively which indicates the melting of the excipients. The melting peaks of the lipids during storage slightly shifted below 40 °C. Based on the comparison of the enthalpy of fusion, remarkable changes were detected. In the case of DS1 the value decreased from 47.26 J/g to 14.61J/g., while for DS2 and DS3, such changes were not recorded. The melting range of the diclofenac sodium also shifted to lower temperatures for DS1, DS2 and DS3 and this phenomenon occurred at the stored samples as well.

ACP also decreased the melting range and the fusion of enthalpy of the GC and CSA, in all cases. The APIs melting range was also decreased, however as the samples containing more and more CSA, the melting peaks got closer to the peak of the pure drug.

The melting peak of the MNZ in our study was found to be at 162.32 °C. In contrast to the previous formulations only slight decrease of the melting point was observed with the MNZ capsules. The melting range broadening was detected only in the case of the stored MNZ1 compared to the fresh one.

3.1.6. PXRD study

Our pure actives and our freshly prepared samples of formulations were tested by powder X-ray diffraction. As presented, pure DS were in its crystalline form, the diffractogram is characterized by the presence of principal diffraction lines at 7.3, 8.5, 11.0, 12.5, 15.0, 16.0, 17.0, 19.5, 23.5 25.0 and at 27.5° (2θ). In DS1 formulation lack of characteristic peaks were presented of diclofenac. The pure ACP gave the following diffraction peaks: 12.1, 13.75, 15.5, 16.7, 18.1, 20.4, 21.5, and 24.4 at 2θ. Fresh ACP1 presented two extra peaks, namely 19.2 and 23.5°, which are characteristic to the Gelucire 50/13. Fresh MNZ1 sample was also compared with GC and pure MNZ too. As the result of these measurement undissolved fraction of the pure MNZ were still present in the sample.

3.1.7. HPLC analysis of degradation products

The separation and the analysis of the degradation product of DS were only detectable in the case of concentrated solutions (not more, than 10 times dilution with methanol). The retention time of the degradation product (small peak) was at 5.6 mins (λmax= 265 nm), before the main peak of the API (Rt: 9.6 mins; λmax= 275). The AUC values for this impurity was the highest only at 2 years old DS1 samples, the ratio of the AUCs of the impurity was less than 0.5% for each samples.

3.1.8. In vitro drug dissolution

Based on the data it was confirmed that the Gelucire 50/13 alone slowed the drug dissolution, 81.99% of the API dissolved after 500 mins. Blending 5% and 10% CSA to the compositions, DS2 and DS3, resulted prolonged drug release. From the fresh samples 83.85% (DS2) and 83.76% (DS3) of the drug dissolved in 750 mins. After 1 month of storage 82.61% dissolved from DS2 in 750 mins, interestingly 70.73% dissolved from

Comparing the fresh and stored release data of capsules with Gelucire 50/13 alone (ACP1) in 500 min 79.48% and 91.00% of the drug dissolved, respectively. Incorporating 5% and 10% of CSA into the matrices (ACP2 and ACP3) slowed the drug dissolution further. 81.98% and 75.30% of the drug dissolved from the fresh and the stored ACP2 in 600 minutes, while the release profiles of the fresh and stored ACP3

were practically identical, in 850 minutes 81.53% and 81.68% got released from the dosage form.

From the fresh sample of MNZ1 81.39% of its drug content was released in 500 minutes, after 1-month storage the dissolution did not changed remarkably, 80.50% dissolved from the capsules. With 5% CSA in the matrices (MNZ2) the drug release was very similar at start, 80.66% got released in 500 minutes, after storing the samples the dissolved drug fraction decreased to 71.47%. In the case of MNZ3, the drug release did not alter.

3.1.9. Mathematical analysis of the drug release profile

First order model was found to be the best model describing the drug release from the fresh and the stored DS, ACP and MNZ matrices, R^2>0.99. However, it should be noted that similarity and difference factor calculations of formulation DS3 showed changes after storage, its f1 and f2 was 10.88 and 54.84, respectively. Based on the model independent calculations of the ACP data, all of the dissolution profiles were found to be similar. When the MNZ profiles were compared after storage, the biggest difference was found with composition MNZ2, where f1 and f2 was 10.43 and 57.76, respectively, notably the dissolution profiles can be considered similar. MNZ3 compositions showed no alterations and strong similarity (f2= 89.21) between the release profiles.

3.2. Experimental results of the floating moulded dosage form by melt foaming

3.2.1. Effect of temperature on the viscosity of the molten suspension

53 °C was found to show the highest viscosity values, namely 0.994 (Pa·s), which was suitable for mixing. It was also noticed that during the precise cooling, the viscosity values increased with such a great extent that at 52 °C, the inner cylinder was unable to rotate, freezing of the dispersion occurred. As an optimal temperature to maximize gas entrapment efficacy, 53 °C was chosen and later foam production were done at this temperature.

3.2.2. Density values of the foamed compositions

It was found that M1, M2 and M3 are non-floating compositions, because their densities are higher than 1 g/mL. These compositions were excluded from further investigations. M4, M5, M6 and M7 were successfully foamed with this technology as their density values were below 1 g/mL and as a result, all of the foamed M4, M5, M6 and M7 compositions showed zero floating lag-time in purified water. The lowest density reached was 0.82 g/mL, this belongs to the M6 formulation. This means a 35.6% decrease in the mass, due to the dispersed gas. The average calculated API content in this formulation was found to be 252.3 mg in the average amount of 840 mg.

3.2.3. SEM analysis and void characteristics

On the SEM images, the cavities created in the melt by the dispersed gas phase can be easily distinguished from the matrix of the solidified melt and the crystals of the MNZ are also detectable. The shape of the cavities is typically spherical or spheroidal. Cavities formed by the merging of bubbles may also be present. The cavities formed by merging of bubbles have short channel-like appearance, and they are assumed to originate from mechanically dispersing gas in the melt. The inner surfaces of the cavities are typically smooth, uneven surface can possibly be seen as well, as a result of the solidified but once fluid melt. The solidified melt forms one single phase in which the solid, undissolved crystals of the MNZ are present and the cavities created by the dispersed gas are distributed randomly. The sizes of the voids were found to be 254±83, 193±63; 231±113 and 67±25 microns for M4; M5; M6 and M7, respectively.

3.2.4. Microtomography results

The foaming process step creates a highly porous structure where the molten matrix is loaded with spherical or spheroidal bubbles. The distribution of the bubbles or voids are random. The reconstructed and computed model of the foam structure shows a closed cell structure in which interconnecting voids or deformed bubbles are present. These short channel-like voids could show various shapes, but most of them can be imagined as few chambers or rooms interconnected with tubular passages. However, none of them were found to be opened to the outer environment.

3.2.5. Dissolution and floating properties

During the dissolution tests, all samples of M4-M7 compositions were proven to possess zero-floating lag time and none of them sank before complete disintegration. In the case of completely disintegrated M4 compositions, raft like remnants were present at the top of the aqueous media. M4 was found to release the MNZ in the shortest time, namely 91.07% were dissolved until 3 hours. Water uptake curve of M4 greatly differs from the others. It was observed that the percentage of the water-uptake of this formulation increased until 1 hour, then a maximum uptake was reached at 3 hours. At this time point one of the samples completely eroded, and only two were removed and tested. The average of the percentage of remaining mass of the samples is only 6.56%. M5 released 88.33% of the drug after 5 hours. Regarding its water-uptakes and erosion, only 15.16% of the original mass of M5 was found in the dissolution media, with absorbing 68.97% water from the dissolution buffer. M6 released only 83.27% at 5 hours, while M7 was found to release only 85.79% its MNZ content at 10 hours. M7 adsorbed the least amount of water during this test and showed that the average of 26.92% mass remained after 10 hours.

3.2.6. Drug release analysis and model fitting

Comparison of the release profiles revealed that the drug release from M5 and M6 can be considered similar only (f1 and f2 are 4.92 and 67.87, respectively). When the dissolution efficiencies were calculated it was found that for M4 showed the

fastest release with the value of 88.43%, while for M7, the value of DE was only 57.21%.

None of the models fitted to zero-order model, while the calculations revealed that the release data of all presented formulations fitted best to the Korsmeyer-Peppas model, since the correlation coefficients were all greater than 0.99.

3.2.7. Texture analysis

It was revealed that in the cases of all floating compositions a hard and resistant structure is present in spite of the air entrapment. Applying 45 N of compression load on the foams did not result any cracks or fractures in the dry state at 25 °C. On the other hand, when the compositions were compared, it was found that the deformation of M4 under the constant pressure of the analyser probe for 5 sec is significantly different that the others, $p < 0.0001$. Regarding M4, a softer structure was found. As was expected on the basis of the erosion studies, M4 samples could be tested at only 1 hour. M4 samples presented small dry and resistant cores inside, the compression force of 45N resulted the compaction of this core. M5, M6 and M7 still contained dry, solid cores inside also, but their resistance against the compression force was different. M7 however presented a wetted outer layer which separated due to the compressional test. After 3 hours, all samples of M5, M6 and M7 were compressed and somewhat flattened by the measurement probe. M5 owned to show the least hard structure, while M7 had the most resistant one. After 5 hours, M7 contained only dry and brittle core, and from 2 to 11 sec of the test time, higher load values were recorded. After 7 hours a nearly complete wetting and erosion of the samples resulted similar load-time curves for M5, M6 and M7

4. Discussion:

4.1. *in situ* lipid matrix formation in MR capsules:

The novelty of our experiments was that we investigated the effect of short term heating on the capsule shells. Interestingly a trend was noticed where capsule shell lost their moisture primary in the earlier periods. A possible explanation could be that because of heating gelatine becomes hygroscopic and it has a potential to slow down the rate of moisture loss. Interestingly when the capsules were treated with a relatively short heating at 63 °C, significant difference was found between the groups where the capsules were kept in a close container or where not. The mechanical strength of the capsules can be preserved if preventive step, e.g. closed in fully-filled containers or humidified hot air as heating medium, is applied.

In fracturing test DS1 showed softening during 1-month storage, while the increasing ratio of the CSA in the compositions DS2 and DS3 prevented the softening, no significant changes was measured during storage. Interestingly when the plasticity test was evaluated, alteration was detected upon storage, namely hardening of the DS2 and DS3 samples. The difference between the findings can be explained by the distinct nature of the texture analysis. While the plasticity tests are compressional tests where the whole sample is deformed, the 3-point bend is a fracturing test, where defined points of the sample is fixed and the force to break samples in halves is recorded. Structure alterations, caused by lipid aging or reorganisation of the chains of PEG or fatty acids might be the root cause. As a summary, the more CSA added to the powder the harder matrices developed upon storage. To break the weakest matrices (ACP2), the pressure of 571 grams should be used, while for the others, especially the MNZ and DS more than 700 or 1000 grams would be sufficient. These could be noteworthy results from a potential dosage form candidate which production lacks any compressional step.

In the case of DS1 thermal analysis revealed significant decrease in the enthalpy of fusion during storage, which is in concordance with the texture analysis. Increasing amount of CSA prevented this effect in DS2 and DS3, but the melting range of DS decreased in each composition. These findings strongly suggest that there is an interaction among DS and GC. The ACP both in the fresh and stored matrices was at least partially dissolved, as the GC decreases in the different compositions the undissolved fraction of the drug increases. Approximately 50% of the original amount of ACP remains in its crystal form. The melting peak shifts was the mostly negligible in the cases of MNZ matrices, but a considerable amount remained in its crystalline state in the matrices.

Based on the NIR measurements it can be stated that melting results development of intermolecular associations among the moulded excipients and the EC, possibly due to the formation of hydrogen-bonds. This association strengthened while the samples were stored until the measurements. Signs were detected suggesting that DS also involved in this molecular association, while no were for ACP and MNZ.

The PXRD measurements demonstrated that only characteristic peaks of Gelucire were present in DS1. Based on the disappearance of the crystalline diclofenac sodium, we can conclude that with our method of manufacture solid solution of diclofenac was formed. Regarding the PXRD measurements of the ACP1 and the pure active we detected no phase transition of the active ingredient on the molten matrix. Based on these result we can state that Form I (monoclinic) acetaminophen was in our samples and the active was also presented in its undissolved form. According to the biowaiver monograph of this active ingredient, for the metronidazole base only, polymorphism has not been reported. The PXRD analysis proved, MNZ is present in the molten matrix in its crystalline form.

HPLC assay of DS matrices revealed negligible chemical degradation products or impurities of the API, fulfilling the requirements of the European Pharmacopeia thus no further identification was performed.

As proved by the dissolution profiles Gelucire 50/13 alone provided a prolonged drug release from the matrices. An earlier study showed that diclofenac-Gelucire 50/13 solid dispersion provides faster drug release compared to the physical mixture. The reason why drug release has accelerated during storage in the case of DS1 is that the API dissolved in the lipid matrix or because of the ageing, fatty acid or PEG chain reorganizations of the Gelucire 50/13 as the main meltable component. The interaction between DS and GC observed in thermal analysis can explain the accelerated dissolution. Interestingly ACP and GC have a similar interaction. This is in concordance with a previous observation when ACP was added to hot and molten GC and stored for weeks. Rapid release compared to the fresh samples was also noticed. Based on the drug dissolution data we can state that as the APIs water solubility increases the dissolution rates from the presented formulations also increased. As release model calculations showed, First-order model was found to describe the drug dissolution from all of the matrices. The First-order describes drug release through diffusion mechanism, and it has been used to describe drug dissolution from systems such as matrix tablets containing water soluble drugs. I would also like to emphasize that drug release from Gelucire 50/13 could be due to matrix erosion and swelling. However, the effect of ageing was investigated before, no publications was found whether the alterations can be prevented by excipients.

4.2. Floating moulded dosage form by melt foaming:

During our study we applied a steel mould to study the foamed matrices and to discover its main pharmacological and physicochemical properties. The main matrix components melt below 70 °C; this temperature is a key factor. This temperature is the maximum filling temperature of hard gelatine capsules. These components are also favourable from a technological aspect that they can exist in semi-solid state also, in which state, due to the high viscosity, dispersing gas into the molten dispersion leads to a more efficient foam formation. Optimal temperature with sufficient ability to be moulded and to entrap gas in our PEG 4000 and SA based matrices was found for this polymer at 53 °C.

In this study we demonstrate that four different compositions with zero floating lag time were prepared with our apparatus in batch mode by filling the foamed and hot dispersions into metal mould. Based on our result we can state that to sufficiently decrease the density of the dispersions, at least 5% SA was also elementary, 2.5 m/m% Labrasol alone could not decrease the densities below the density limit of 1.00 g/mL. However, we do not exclude the possibility that with increased agitation speed and shear force coupled with controlled gas-injection PEG-API-gas dispersions can be created. The HLB value of the SA is 15. Beside its numerous application as a dissolution retardant in oral hydrophobic matrix systems, SA can be used to create foam from o/w emulsions. The authors states based on the results of the experiments that SA contribute to the easier foamability by accumulating at the surface of the air bubbles, thus creating an apolar layer which surrounds the dispersed gas phase. Similar mechanism has been earlier described and discussed when diary emulsions were foamed with a similar whipping technique.

While combining Labrasol with SA, results an increase in the void sizes. On the other hand, open-cell structures were not created, but short and interconnecting clusters of spherical voids developed in all cases. None of the pictures showed that the dispersed crystals of MNZ were involved in bubble entrapment of interphase stabilization. MicroCT scans on M7 foam structure confirmed a presence of a complex spongy structure. The foam structure however is not surrounded by a hard and thick, bubble-free shell-layer or outer jacket. Air filled voids are randomly distributed throughout the whole matrix.

When the foamed compositions were investigated regarding their release characteristics we found that the Labrasol increased the erosion and dissolution rates due to its good ability of micelle solubilisation. Regarding the water-uptake studies the PEG matrix absorbs water and swelling of the polymer chains develop, however we should also mention, that water can also penetrate and fill up the micron sized cavities. On the other hand, the whole inner pore system could not be completely flooded due to the shortness of the interconnections. This is favourable, since gas is entrapped in separate chambers providing continuous floatation. Dissolution of MNZ when compared to the matrix erosion curve suggests that drug release is mainly controlled by erosion. It can be stated on the basis of the presence of MNZ crystals in the moulded matrix. On one hand, it is noteworthy to mention that the diffusion-path of the dissolved drug is elongated since air-filled voids are impermeable for the dissolution media.

Kinetic model analysis revealed that Korsmeyer-Peppas model fitted best to dissolution data: This kinetic model is used to analyse drug release of polymeric formulations when more than one type of release phenomena is involved. Release exponents of M4 and M5 were 0.9414 and 0.9759 indicate Super Case-II transport due to the cylindrical shape, while for M6 and M7 the n values were 0.7162 and 0.6889 corresponding to anomalous or non-Fickian diffusion transport. According to these findings, beside the rates of drug release, the mechanism is modified by Labrasol, as well. A possible explanation could be that Labrasol works as a plasticizer in the matrix

therefore a rapid water uptake and matrix is coupled with the increased API concentration in the inner pores, due to the solubilisation of MNZ.

This also suggests differences in the speed of structural weakening of the foams as seen during texture analyses. Plasticizing the PEG and SA chains together with a higher rate of water imbibition resulted the fastest erosion of M4. Plasticizing effect could be the reason of the significantly softer texture of the dry M4 at 25 °C. However, 10% of SA was able to develop a more ordered structure, resulting a harder and more resistant matrix. SA not only delay disintegration and increase hardness, but due to its edible nature shows advantageous properties as oral release retardant.

5. Conclusion:

In this study we developed a new method and technology to alter drug release from HGCs without dissolving or dispersing the API in molten material and liquid-fill the shells. We successfully extended the drug release by *in situ* melting and lipid matrix formation. Capsule studies proved that heating conditions must be considered cautiously, but short term heating can be performed on HGCs without becoming brittle. Texture analysis revealed that formed matrices are resistant to bear the stress of further technological processes, such as transferring from or to bulk containers of bags and blistering. Thermal analysis confirmed that no thermal degradation occurred at 63 °C, the lowest temperature where degradation started was at 200 °C. This platform may be useful to pharmaceutical technologists and researchers to turn to innovative results.

The second presented technology describes a novel method to foam hot and molten dispersions on atmospheric pressure. This technology is directly applicable to produce floating, low-density moulded dosage forms. Undissolved drug in the molten dispersion does not affect the continuous buoyancy up to 30%. MNZ was released mainly by the erosion of the PEG-SA matrix, however Labrasol as a non-ionic solubilizer alter the dissolution mechanism by increasing drug solubility and increasing the rate of water-uptake. We applied several methods to characterize the properties of foam matrix system. SEM pictures and microCT scans confirmed that air bubbles form spherical closed-cell structure where clusters of interconnecting voids can be found. Texture analysis confirmed that SA in our matrices inhibit disintegration and maintain mechanical resistance in acidic buffer at 37°C. The temperature of the technology is ideal for hard capsule filling to prolong gastric residence time.

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List of publications:

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1. **Vasvári, G.**, Haimhoffer, Á., Horváth, L., Budai, I., Trencsényi, G., Béres, M., Dobó Nagy, C., Váradi, J., Bácskay, I., Ujhelyi, Z., Fehér, P., Sinka, D. Z., Vecsernyés, M., Fenyvesi, F.: Development and Characterisation of Gastroretentive Solid Dosage Form Based on Melt Foaming.
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