Scientific paper

Study of Immediate Release Spherical Microparticles Containing Clarithromycin using a Hot-melt Fluid Bed Technique

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Abstract

The aim of the study was to evaluate a hot-melt technique for preparation of immediate release spherical microparticles containing clarithromycin with acceptable characteristics and process yield. A modified fluid bed apparatus with rotor insert was used to prepare spherical microparticles in the size range of 125–355 μm. Poloxamer 188, PEG-32 glyceryl laurate (Gelucire 44/14) and a mixture of polyethylene glycol (PEG) 4000 with PEG 400 were used as meltable binders. Key process parameters were identified and optimized and their influence on process yield and microparticles characteristics was determined. Microparticles with poloxamer 188 and PEG exhibited relatively good mechanical properties. Process yield was around 70% and 60% in the case of PEG and poloxamer 188 respectively. Microparticles prepared with PEG-32 glyceryl laurate exhibited poor mechanical properties and process yield compared to other microparticles. The process was shown to be limited by the bed temperature, exhibiting the best process stability with poloxamer 188 followed by PEG and PEG-32 glyceryl laurate. Dissolution rate and equilibrium concentration of clarithromycin released from prepared microparticles was improved compared to similar particles prepared by wet granulation.

Keywords: Hot-melt; Fluidized bed; Immediate release; Polyethylene glycol; PEG-32 glyceryl laurate; Poloxamer 188

1. Introduction

Hot-melt techniques employ molten or softened materials to act as binders in the preparation of solid dosage forms such as tablets, granules, pellets and microparticles or use such materials for coating of pharmaceutical formulations. The methods allow the preparation of either immediate or controlled release dosage forms, depending on the materials employed.[1,2] Meltable materials which can be employed include suitable polymers, waxes or other lipid-based materials. These substances are melted during the formulation procedure and solidify during or at the end of the technological process. Such an approach delivers several advantages, most notably the absence of solvents in the formulation preparation. This allows the processing of water sensitive active ingredients and reduces costs and time of production since there is no need for drying of the product. Furthermore, such method avoids issues of residual solvents which are particularly problematic with organic solvents. The most commonly used methods include hot-melt extrusion, hot-melt agglomeration in high shear mixing and formulation of simple melt dispersions.[3–7] The application of the fluid bed system for preparation of formulations based on hot-melt technology was first described in patent literature by Heinemann and Rothe in 1973 and in scientific literature in 1990 by Jozwiakowski *et al.*[8,9] Fluid bed systems have been used for hot-melt granulation as well as hot-melt coating, where melts were applied as coating to ensure prolonged release of active substances.[10,11] Immediate release granules prepared by hot-melt fluid bed can have different size distribution and morphology compared to the granules prepared by more commonly used hot-melt processes (e.g. hot-melt high shear granulation), although solid state characteristics and dissolution seem to be process independent.[12] The hot-melt

granulation processes have been assessed and characterized practically as well as computationally using several different binders, including polyethylene glycol, poloxamer 188 and 407, PEG-32 glyceryl palmitostearate (Gelucire 50/13) or glyceryl monostearate.[13–22] Processes have been studied in terms of mechanism of agglomerate growth and the influence of binder droplet size, viscosity, starting material particle size and type of binder used. Particle size and particle size distribution of final granulate has a profound effect on final dosage forms assay and content uniformity as well as behavior of powder mass during further processing.[21,23] Thus a hot-melt method which would result in suitable particles size and particle size distribution is desired in order to be commercially applicable.

In our work, reported here, we prepared spherical microparticles ranging in size from 125 to 355 μm using fluid bed rotor technology. Different materials were used as binders to prepare particles with immediate release profile. The influence of process parameters and possible optimizations or limitations of employed binders were investigated. Prepared microparticles were characterized in terms of dissolution rate and saturation solubility of clarithromycin, a model drug used due to its low and pH dependant water solubility.[24]

2. Experimental

2. 1. Materials

Microcrystalline cellulose (MCC) (Avicel PH 105, FMC, USA) was used as filler and starting material. Polyethylene glycol (PEG) 4000 (Clariant GmbH, Germany), poloxamer 188 (Lutrol F68, BASF, Germany) and PEG-32 glyceryl laurate (Gelucire 44/14, Gattefosse, France) were used as meltable binders. PEG 400 (Fluka, Germany) was added to reduce the friability of microparticles when PEG 4000 was used as binder. Lactose NF mesh 200 (DMV, The Netherlands) was used in preparation of reference clarithromycin granules. Clarithromycin was from Ind-Swift Laboratories, India.

2. 2. Differential Scanning Calorimetry

Starting materials used as binders were characterized by differential scanning calorimetry (DSC), either alone or in a 1:1 physical mixture with the active ingredient. DSC measurements were performed on a Pyris 1 DSC (Perkin Elmer, USA) equipped with the Intracooler 2P cooling accessory. Accurately weighed samples (5–10 mg) were placed in standard aluminium pans and covered with a pierced lid. A heating rate of 10 K/min was used with a nitrogen flow rate of 20 mL/min. Prior to measurement, all samples were heated to 100 °C and subsequently cooled to 0 °C at a rate of 10 K/min to ensure comparable and relevant results.

2. 3. Equipment Setup for Hot-melt Agglomeration

Experiments were carried out in a modified Glatt GPCG-1 apparatus (Glatt, Germany), equipped with a rotor processing insert. The processing chamber was a standard GPCG-1 chamber with the lower part equipped with a smooth rotor plate (28.7 cm in diameter) and a volume of 7.2 L. The upper expansion part had a volume of 24.2 L. The chamber was enclosed in a custom built insulating housing to ensure constant temperature conditions. The spraying nozzle was encased in a custom built polytetrafluoroethylene casing identical to the original stainless steel casting to prevent melt solidification in the nozzle and to shield the product from an overheated nozzle. A nozzle with a 1.2 mm diameter orifice was used (Düsen-Schlick GmbH, Germany).

An electrically heated tube (GLATT Systemtechnik GmbH, Germany) was used to raise the atomizing air temperature to the desired value. The binder melt was thermostated at a constant temperature with a magnetic stirrer/heater coupled with a digital thermometer (IKA basic, IKA, Germany). The binder melt was then pumped to the processing chamber using a Flocon 1003 peristaltic pump (Petro gas Ausrüstungen, Germany) and silicone tubes, which were heated with heating tapes (Cole Parmer, USA) controlled by heating controller (Digi-Sense, Cole Parmer, USA).

2. 4. Preparation Procedure of Spherical Microparticles

Batches comprising 150 g of the active ingredient and 150 g of MCC were used in each experiment. Prior to preparation of microparticles the apparatus was heated to a set temperature, shut down and powder mixture was transferred into the processing chamber. The inlet air temperature was set to an appropriate value for the binder being used and the inlet air speed was set to 2 m/s (~ 60 m^3/h) in all experiments. The filter was shaken in alternate halves at 3 second intervals for 5 seconds without interrupting the fluidization and binder spraying. Melted binder was thermostated to a set temperature during the entire process and sprayed onto the fluidized powders at a constant rate. The rotational speed of the smooth rotor plate was set to 1250 rpm. Atomizing air pressure and atomizing air temperature were set in accordance with binder melt properties to ensure suitable binder droplet size. Inlet air temperature, starting chamber temperature and spray rate of binder melt were optimized for each binder separately. The experiments were terminated after the required amount of binder was sprayed onto the powder mixture. In cases when subsequent spheronization was performed, the process parameters (rotor plate speed, inlet air temperature …) remained unchanged.

2. 5. Reference Granules Preparation

Pure drug could not be used for saturation solubility and dissolution rate testing due to its extreme hydrophobicity which prevented proper mixing of the drug with the test media. Therefore reference granules with clarithromycin were prepared by wet granulation. Meltable binders were replaced with lactose, which served as hydrophilic binder. Equal amounts of clarithromycin and MCC were mixed with lactose to obtain a composition containing 40% active substance. The composition of the prepared mixture was similar in regard of the clarithromycin content to the microparticles prepared with the hot-melt method, where the clarithromycin content was 36% for PEG, 39% for PEG-32 glyceryl laurate and 40% for Poloxamer 188 microparticles. Water was added to powder mixture to obtain a wet mass of suitable consistency, which was subsequently pushed through a 700 μm sieve. The resulting wet granulate was dried for 4 hours at 45 °C. Size fraction of granules between 125–355 μm was used in all dissolution experiments.

2. 6. Sieve Analysis

Sieve analysis of the final product was performed using an AS200 basic vibration sieve (Retsch, Germany). Sieves with opening sizes of 125, 180, 250, 355, 400, 500 and 710 μm were used. Sieving was performed for 10 minutes at amplitude of 2 mm. Useful yield (γ_{ok}) was expressed as wt/wt ratio of the size fraction mass (125–355 μm) to the starting material mass. Particles with sizes from 125–355 μm were used for all further analysis.

2. 7. Particles Friability

Friability of particles was assessed using an Erweka TA friability apparatus (Erweka, Germany) equipped with an Abrasion drum (Erweka, Germany). Precisely 10 g of particles were accurately weighed and placed into the drum together with 20 g of glass beads and rotated for 10 minutes at 25 rpm. After rotation, the glass beads were removed and the resulting particles were exposed to a mild air current to remove adhered powders before being accurately weighed. Friability was calculated as a mean of three measurements using Eq. (1) where m_a represents the mass of particles after the test and m_b the mass of particles before the test:

$$friability(\%) = \frac{m_b - m_a}{m_b} \cdot 100 \quad (1)$$

2. 8. Optical Evaluation

Photographs of selected samples were taken using an optical stereo microscope Olympus SZX12 (Olympus, Japan) equipped with a digital camera (DXC-95OP, Sony, Japan) and connected to a computer with image processing software (analySIS, Soft imaging systems, Germany).

2. 9. Solubility and Dissolution Studies

Pure drug could not be used for saturation solubility and dissolution rate due to its extreme hydrophobicity which prevented proper mixing of the drug with the test media. Therefore reference granules with clarithromycin were used as reference in the evaluation of microparticles prepared by the hot-melt method.

For saturation solubility studies, microparticles containing 300 mg of active ingredient were weighed and dissolution experiments were carried out in triplicate in 200 mL of phosphate buffer with pH 6.8 thermostated at 37 °C in non-sink conditions. At specified time points 1 mL samples were withdrawn, filtered through 0.45 μm pore filter (Sartorius, Germany) and analyzed using the HPLC system described below.

For dissolution rate studies, microparticles containing 150 mg of active ingredient were weighed and dissolution experiments were carried out in triplicate in sink conditions in 900 mL of dissolution medium.

Dissolution experiments were carried out on a VanKel VK7000 dissolution apparatus (USA) equipped with standard glass vessels and paddles. Paddle rotating speed was set to 50 rpm in all experiments. Phosphate buffer with pH 6.8 thermostated at 37 °C was used as dissolution medium. At specified time points 1 mL samples were withdrawn, filtered through 0.45 μm pore filter (Sartorius, Germany) and analyzed using the HPLC system described below.

The HPLC system (Knauer, Germany) was combined with a Midas autosampler and column oven (Spark Holland, The Netherlands). A Licrosphere silica Si-100 150 × 4.6 HPLC column (Thermo, UK) was installed in the oven and thermostated at 30 °C. Mobile phase, consisting of phosphate buffer adjusted to pH 6.8 and methanol (35:65 v/v), was pumped through the system at a constant flow rate of 1 mL/min. A UV detector for the detection of clarithromycin was set to 210 nm.

3. Results and Discussion

3. 1. DSC Analysis of Binders and their Mixtures with Clarithromycin

DSC curves of dispersions of active substance in binders can indicate possible interactions between these substances, which can influence initial technological process temperature settings (e.g. lowering of melting point of the binder) or disclose total incompatibility with the process (e.g. formation of eutectic mixture with melting point below ambient temperature). DCS curves recorded

for a mixture of PEG 4000 and PEG 400, poloxamer 188 and PEG-32 glyceryl laurate and their mixtures with clarithromycin are shown in Figure 1. Since there are no significant changes in DSC curves for mixtures of clarithromycin with binders compared to pure binders, it was concluded that there are no significant interactions between clarithromycin and binders which could influence initial temperature settings as regard to the binder melting point or otherwise limit the process. A melting point depression can be observed for the melting peak of clarithromycin when mixed with the binders, which indicates mixing of the active substance with the binder melt, a process already described in the literature for other active substances and PEG.[25] Based on these findings we can conclude that there are no significant interactions between the active substance and the binders in the final microparticles.

3. 2. Preparation of Microparticles

The preparation of microparticles was carried out in a modified Glatt GPCG-1 apparatus equipped with a rotor granulator process chamber. Contrary to the previous reports,[26] while conducting preliminary experiments we did not observe any difference between a smooth or longitudinal grooved friction plate, so the former was used rotating at 1250 rpm in all experiments. The starting mixture, which was transferred to a preheated rotor granulator chamber at the beginning of the experiments, always consisted of 150 g of clarithromycin and 150 g of MCC. Several experiments were carried out for each binder and the resulting optimal process parameters in regard to the useful yield (i.e. particle size from 125 to 355 μm) and friability (as low as possible) for each binder are shown in Table 1. Optical micrographs of prepared microparticles are shown in Figure 2.

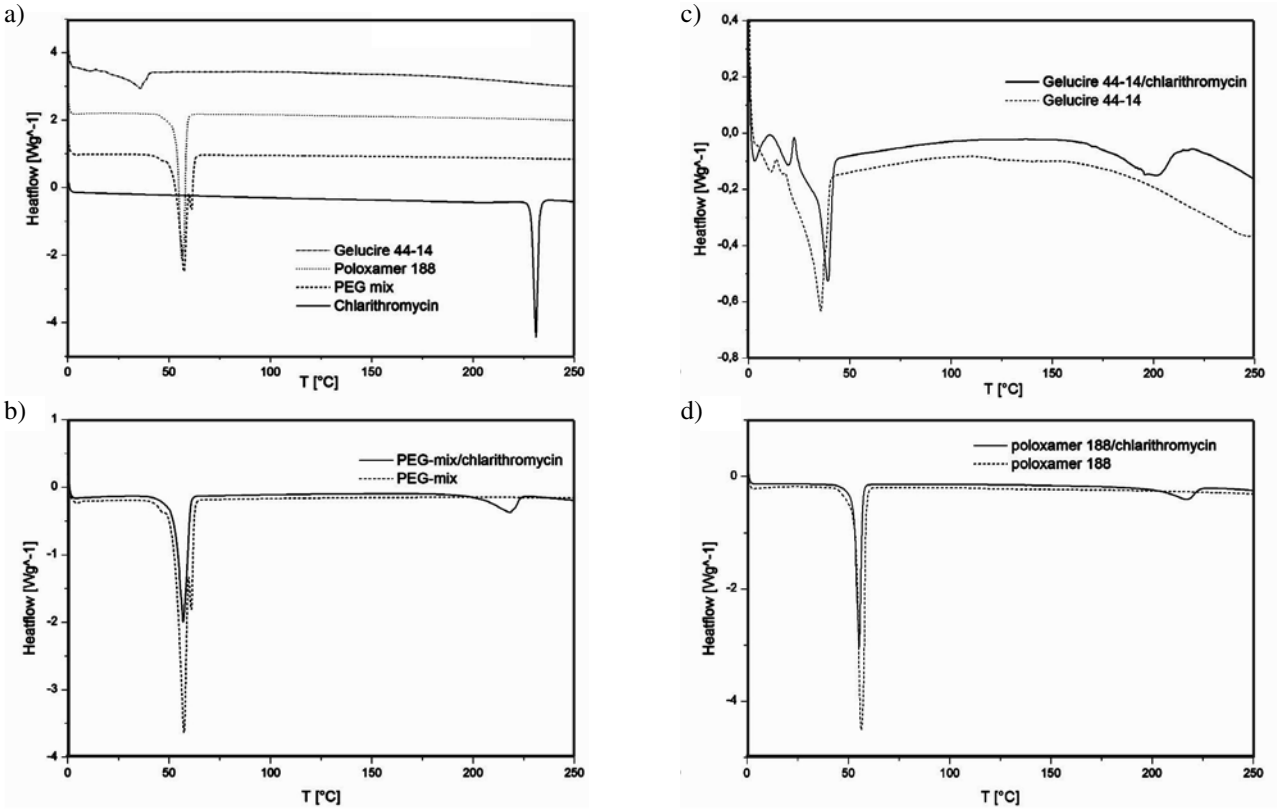

Figure 1: DSC curves for clarithromycin and different binders (A) and their mixtures with clarithromycin in ratio 1:1 (B, C, D). Gelucire 44–14 is a trade name for PEG-32 glyceryl laurate.

Table 1: Process parameters: inlet air temperature (T_{in}), starting chamber temperature (T_{pre}), binder spray rate (V_{sp}), atomization pressure (P_{at}), atomization air temperature (T_{at}), binder melt temperature (T_{melt}), spheronization time (t_{sph}), mass of applied binder melt (m_{bind}) and product characteristics: friability (F) and yield of particles from 125 to 355 μm (γ_{ok}) for microparticles prepared with different binders.

Binder	T_{in} [°C]	T_{pre} [°C]	V_{sp} [g/min]	P_{at} [bar]	T_{at} [°C]	T_{melt} [°C]	t_{sph} [s]	m_{bind} [g]	**F** [%]	γ_{ok} [%]
PEG	52	49	14.2	3.0	180	85	70	120.5	4.70	68.2
PEG-32 glyceryl laurate	43	39	11.5	3.0	175	75	0	81.0	9.32	28.9
Poloxamer 188	55	51	9.8	3.5	190	90	59	71.2	4.57	59.1

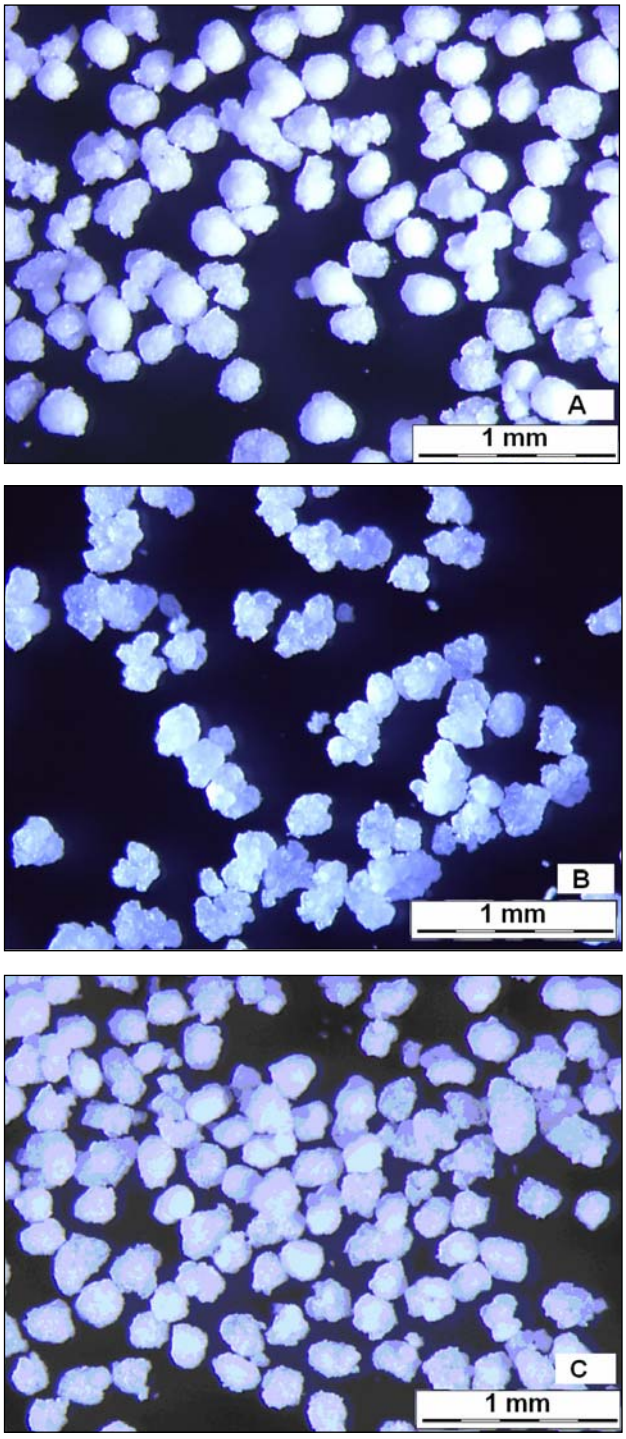

Figure 2: Pictures of microparticles prepared with PEG (A), PEG-32 glyceryl laurate (B) and poloxamer 188 (C).

When PEG 4000 alone was used as a binder, the resulting microparticles exhibited high friability (data not shown). Therefore a mixture of PEG 4000 and PEG 400 in the ratio 22:3 (wt/wt) was used in all cases.

The bed temperature was found to be the main limiting factor in the process of microparticles preparation. This was most evident when PEG-32 glyceryl laurate was used as a binder. When the bed temperature rose above 42 °C, a quick and widespread agglomeration occurred resulting in a useless batch. In the case of PEG and poloxamer the critical bed temperature was 52 and 55 °C, respectively. The binder melt was sprayed constantly in all the processes until the product temperature reached critical bed temperature. High bed temperature, i.e. close to critical bed temperature, allows for better mobility of the binder, resulting in favorable granules characteristics, already described by others.[14,27] When the bed temperature is high, the molten binder solidifies slowly and therefore exhibits increased mobility. During the solidification time the molten or semisolid binder allows for densification and reshaping of the granules and more homogenous distribution of the binder, resulting in more compact and less friable particles. At higher product temperatures the sphericity of the particles is also improved due to greater reshaping and densification of the particles. Considering all process parameters, inlet air temperature, starting chamber temperature and binder spray rate were found to have the strongest influence on the bed temperature, since these are the main parameters that introduce the heat transfer (inlet air temperature, binder spray rate) or set the initial level of heat energy in the system before spraying the binder (starting bed temperature). With the increase in these parameters the time to reach the critical bed temperature is decreasing, as can be seen from the Figure 3.

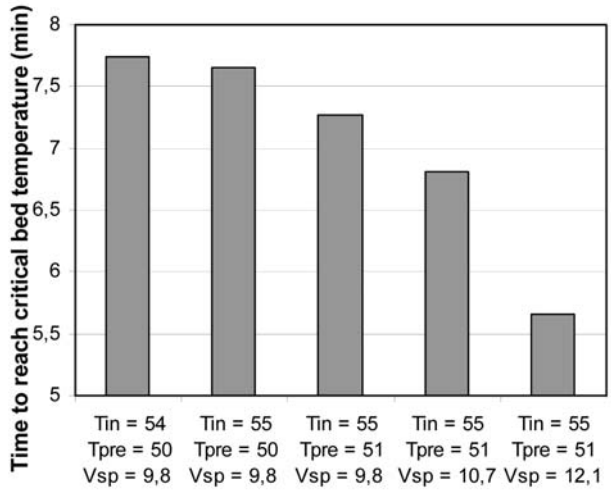

Figure 3: Time to reach critical bed temperature in dependence to the changes in inlet air temperature in °C (T_{in}), starting chamber temperature in °C (T_{pre}) and binder spray rate in g/min (V_{sp}) with poloxamer 188 as binder.

The maximum amount of PEG which could be incorporated into the particles was significantly increased and was around 34% compared to 28% in the previous reports.[25] The amount of incorporated PEG in this study al-

so exceeded the maximum reported amount of binder that can be incorporated into granules by a fluid bed granulator, which is 30%.[28] Magnitude of the shearing forces in the process equipment is in our findings not the only factor limiting the maximum amount of the binder which could be incorporated into the granules produced by hot-melt granulation, as suggested previously.[25] Better control of the bed temperature and gradual addition of the binder (as in the example of fluid bed granulator) probably also play an important role in the hot-melt process.

3. 3. Solubility and Dissolution Studies

Microparticles prepared with PEG, PEG-32 glyceryl laurate and poloxamer 188, as well as the reference granules prepared by standard wet granulation procedure were used to determine the solubilization effect of the binder. Constant levels of clarithromycin in dissolution media were reached approximately after 120 minutes using non-sink conditions (Figure 4). Saturation solubility of clarithromycin from reference granules was, as expected, similar to that of pure substance in the dissolution media as reported previously.[24] Saturation solubility of clarithromycin was increased 20% in the case of microparticles with PEG and PEG-32 glyceryl laurate and 40% in the case of poloxamer 188. Concentration of clarithromycin was stable during 240 minutes and did not decrease as it is usually the case with supersaturated solutions. The increase in the concentration is due to the solubilization effects of the excipients as extensively described in the literature and is a function of the concentration of the excipient.[29] Solubilization capacity for clarithromycin is greater when poloxamer is used compared to the PEG and PEG-32 glyceryl laurate, as already described for other poorly soluble active ingredients.[29] Furthermore, increase in solubility should lead to increased dissolution rate according to the Noyes–Whitney equation and may play and important role in increasing the bioavailability of the poorly soluble active ingredients.[30]

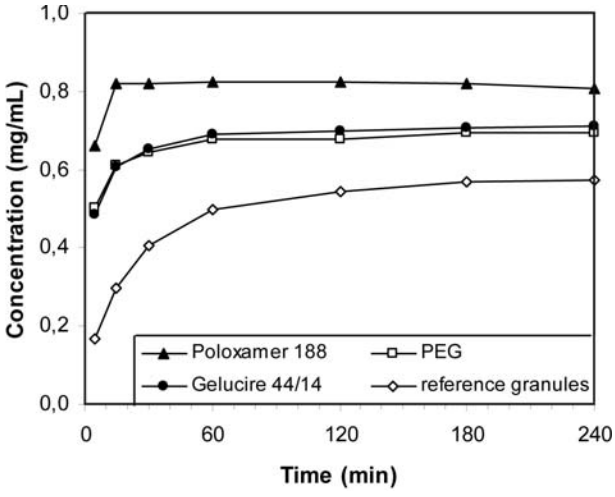

Figure 4: Concentration vs. time of clarithromycin released in phosphate buffer pH 6.8 from microparticles prepared with poloxamer 188 (▲), PEG (□), PEG-32 glyceryl laurate (Gelucire 44/14) (●) and reference granules (◇). Each point represents the mean of 3 determinations. Relative standard deviation was below 4% in all cases.

Dissolution rate of clarithromycin from microparticles with PEG, PEG-32 glyceryl laurate and poloxamer 188 was significantly increased in comparison to reference granules prepared by standard wet granulation procedure (Figure 5). All tested samples had the particle size range between 125 to 355 μm to ensure similar surface for the dissolution. Microparticles prepared with the hot-melt method showed immediate release of the active substance with more than 80% of active substance released in 15 minutes and complete release of incorporated substance after 60 minutes. Release of active substance was much slower from granules of comparable size prepared by wet granulation with lactose. Only 35% of the active substance was released in 15 minutes and subsequent release of active substance was too slow to reach complete release after 240 minutes. Incorporation of lactose as binder into reference granules was intentional, since it is a hydrophilic binder soluble in water and thus comparable to the meltable binders used. As such, lactose did probably have an influence on the increase of the dissolution rate of the active substance compared to the pure substance due to better dispersion of the drug particles, a phenomenon well described in the literature.[31,32] However, this increase was low compared to the meltable binders used, probably due to better wetting and amphiphilic properties of these binders compared to lactose. Since DSC measurements (Figure 1) showed no change in the melting peaks of the binders used in the hot-melt process and expected changes in the melting peak of the active substance, the increase in the dissolution rate can not be attributed to drug-polymer interaction. Furthermore, dissolution rate is probably not influenced by the changes in solubility due to the influence of the excipients. Although we have shown in the saturation experiments that the excipients have an influence on the solubility of the active ingredient, we must not forget that this is a concentration related phenomenon. Since the concentration of the excipients in the dissolution medium is 9 times lower compared to the saturation solubility experiments, this concentration is probably too low to significantly influence the solubility of the active substance. However, to put the saturation solubility data in the true perspective, one must consider the *in vivo* conditions, where the amount of water is usually below the volume used in the saturation solubility tests[33] and therefore the role of excipients in the dissolution rate is greater. The most probable explanation for the increase in the dissolution rate in our experiments is the improvement of the wettability of the active ingredient due to the hydrophilicity of the excipients and their in-

timate contact with the active ingredient, as already described in the literature.[34]

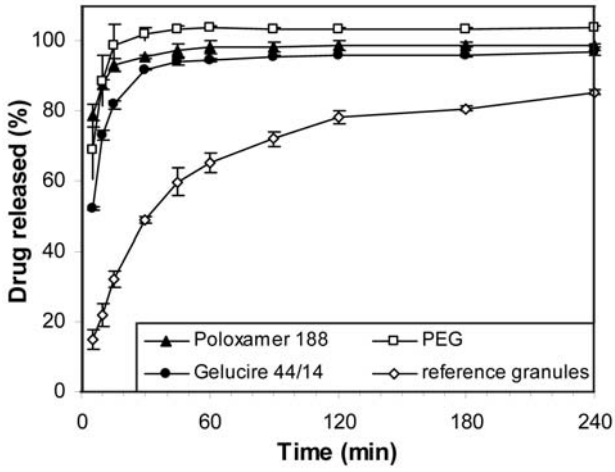

Figure 5: Dissolution rate of clarithromycin at pH 6.8 from microparticles prepared with poloxamer 188 (▲), PEG (□), PEG-32 glyceryl laurate (Gelucire 44/14) (●) and reference granules (◇). Each point represents the mean of 3 determinations.

4. Conclusions

Spherical microparticles ranging from 125 to 355 μm were prepared using a modified rotor insert equipped fluid bed apparatus with either PEG 4000 and PEG 400 mixed in a 22:3 wt/wt ratio, PEG-32 glyceryl laurate, or poloxamer 188 as a molten binder. Bed temperature was the major limiting factor for microparticle preparation and was influenced by inlet air temperature, starting chamber temperature and spray rate of molten binder. The bed temperature was also dependant upon the binder used. Microparticles prepared with PEG-32 glyceryl laurate exhibited poor mechanical properties and process yield compared to other microparticles. The maximal amount of binder that can be incorporated into particles was increased compared to the previous reports, probably due to relatively high shearing forces in the equipment used and also better control of the bed temperature and gradual addition of the binder. The dissolution rate of clarithromycin from the microparticles prepared with meltable binders was significantly increased compared to reference clarithromycin granules. Saturation solubility of clarithromycin was also influenced by the meltable binders used and was increased compared to the reference granules. According to the literature, increase in the saturation solubility, dissolution rate and increased amount of hydrophilic binder that can be incorporated into microparticles are good prediction factors for increased bioavailability of poorly soluble drugs loaded into the microparticles.

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Povzetek

Namen raziskovalnega dela je bil razviti postopek na osnovi talin za izdelavo sferičnih mikrodelcev klaritromicina s takojšnjim sproščanjem. Za izdelavo mikrodelcev v velikostnem razredu 125-355 μm smo priredili aparaturo na principu zvrtinčenih plasti z rotorskim nastavkom. Kot veziva smo preskusili PEG-32 gliceril laurat (Gelucire 44/14®), poloksamer 188 in zmes dveh polietilenglikolov (PEG). Določili smo ključne procesne spremenljivke procesa in jih optimirali v smislu izkoristka procesa in mehanskih lastnosti mikrodelcev. Mikrodelci, pripravljeni s poloksamerom 188 in PEG so v splošnem izkazovali dobre mehanske lastnosti, izkoristek procesa pa je bil okoli 70 % v primeru PEG in okoli 60 % v primeru poloksamera 188. Mikrodelci izdelani s PEG-32 gliceril lauratom so izkazovali slabše mehanske lastnosti in nižji izkoristek procesa v primerjavi z mikrodelci izdelanimi z ostalima vezivoma. Stabilnost procesa je bila odvisna predvsem od temperature produkta v komori in je bila najboljša v primeru poloksamera 188 in najslabša v primeru PEG-32 gliceril laurata. Hitrost raztapljanja in nasičena topnost klaritromicina, sproščenega iz mikrodelcev izdelanih s talinami, je bila večja v primerjavi z mikrodelci izdelanimi s klasično mokro granulacijjo.