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Research paper

A new method for the continuous production of single dosed controlled release matrix systems based on hot-melt extruded starch: Analysis of relevant process parameters and implementation of an in-process control

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A B S T R A C T

Purpose: In the present study, we evaluated a novel processing technique for the continuous production of hot-melt extruded controlled release matrix systems. A cutting technique derived from plastics industry, where it is widely used for cutting of cables and wires was adapted into the production line. Extruded strands were shaped by a rotary fly cutter. Special focus is laid on the development of a process analytical technology by evaluating signals obtained from the servo control of the rotary fly cutter. The intention is to provide a better insight into the production process and to offer the ability to detect small variations in process-variables.

Materials and methods: A co-rotating twin-screw extruder ZSE 27 HP–PH from Leistritz (Nürnberg, Germany) was used to plasticize the starch; critical extrusion parameters were recorded. Still elastic strands were shaped by a rotary fly-cutter type Dynamat 20 from Metzner (Neu-Ulm, Germany). Properties of the final products were analyzed via digital image analysis to point out critical parameters influencing the quality. Important aspects were uniformity of diameter, height, roundness, weight, and variations in the cutting angle. Stability of the products was measured by friability tests and by determining the crushing strength of the final products. Drug loading studies up to 70% were performed to evaluate the capacity of the matrix and to prove the technological feasibility. Changes in viscosities during API addition were analyzed by a Haake Minilab capillary rheometer. X-ray studies were performed to investigate molecular structures of the matrices.

Results: External shapes of the products were highly affected by die-swelling of the melt. Reliable reproducibility concerning uniformity of mass could be achieved even for high production rates (>2500 cuts/min). Both mechanical strength and die-swelling of the products could be linked to the ratio of amylose to amylopectin. Formulations containing up to 70% of API could still be processed. Viscosity measurements revealed the plasticizing effect caused by API addition. Dissolution data proved the suitability of extruded starch matrices as a sustained release dosage form. Monitoring of consumed energies during the cutting process could be linked to changes in viscosity. The established PAT system enables the detection of small variations in material properties and can be an important tool to further improve process stability.

1. Introduction

Pharmaceutical industry shows an increasing demand for adopting continuous processes in their production lines. Continuous processes show many benefits in relation to single batch processes: reduction of waste, energy, and finally costs. A major obstacle for many companies was the lack of insight by regulatory authorities; the attitude changed during the last years and continuous processes become more and more accepted. Decisive facts are a higher product quality and a higher reproducibility [1]. A current problem pharmaceutical manufacturers have to deal with is the processing of increasing amounts of rather lipophilic drugs obtained by selective drug screening [2]. Formulation of new drug delivery systems while maintaining a high bioavailability proves to be more and more problematic. Hot-melt extrusion in contrast to other manufacturing methods shows the advantage of an improved bioavailability by forming a molecular dispersion of an API in the surrounding matrix [3]. In vivo studies carried out by Henrist et al. showed a significantly increased bioavailability of orally administered theophylline-starch extrudates in contrast to a

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commercial available sustained release drug delivery system [4]. It was of particular interest to evaluate the potential of natural based polymers for use as basic substances for sustained release matrices; in relation to petroleum-based structures, nearly unlimited resources are available. Nevertheless, processing of starch without addition of plasticizers often leads to fragile products. During extrusion processing, the starch granules are disrupted and show a loss of crystalline structure. Heating of the material in combination with addition of water leads to a complete gelatinization; hydrogen bonds are destroyed and replaced by water molecules [5]. Blending of natural polymers with opposing properties can improve product stability [6]. High shear rates enforced either by a rough screw design or high rotation speeds can directly affect the molecular weights of the products and lead to a fragmentation of starch [7]. Preparation of granules and pellets still dominate the application field for hot-melt extrusion; in both cases, further processing steps are required to obtain the final products. In most cases, the intention is to manufacture equally shaped spherical pellets. Methods for direct shaping of the still elastic strands are rather limited; calendaring or pellet forming techniques are applied frequently, and novel shaping techniques involve the application of injection molding [8]. First experiments carried out by Keszel et al. could show the use of injection molding for preparing controlled release formulations based on thermoplastic starch [9]. Potential applications already described in literature are the production of oral capsules, oral matrices, implantable matrices, or intra-vaginal inserts [10]. For a high uniformity of the process, micro-injection becomes an interesting further application field. This method is eventually restricted by the fact that temperatures of barrel and mold need to be increased to improve the polymer melt fill in smaller volumes like micro cavities [11]. High pressure and long term exposition to heat may result in drug degradation and limit its application in pharmaceutical industry.

The main aim of our research is focused on the implementation of the new cutting technique into the production line; an important aspect was the establishment of a continuous production. Special focus was laid on the shape of the final single dosed matrices; critical factors influencing the product quality were detected to allow a further improvement of the technique.

Different starches were chosen to cover an extended range of different materials. Depending on the amylose content, physical properties are differing in melt viscosity, die pressure, and die-swelling at the nozzle. An important aspect we could confirm was the ability to process even high viscous material like pea starch or Eurylon®7 without the occurrence of clogging effects.

Another important aspect of our work involves the establishment of a PAT system by evaluating signals obtained from the servo control of the rotary fly cutter. The intention is to offer a better insight into the production process and to provide the ability to detect small variations in process-variables.

It was of particular interest to develop a cost saving continuous production method without applying further stress to the material: circular strands were pre-formed by the attached nozzle of the extruder; after a short cooling phase in a slope, the strand entered a rotary flying-knife cutting where the semi-finished strands were processed into single dosed mono-block forms.

The great advantage of our modified production method is that no further production steps are involved to obtain the final product;

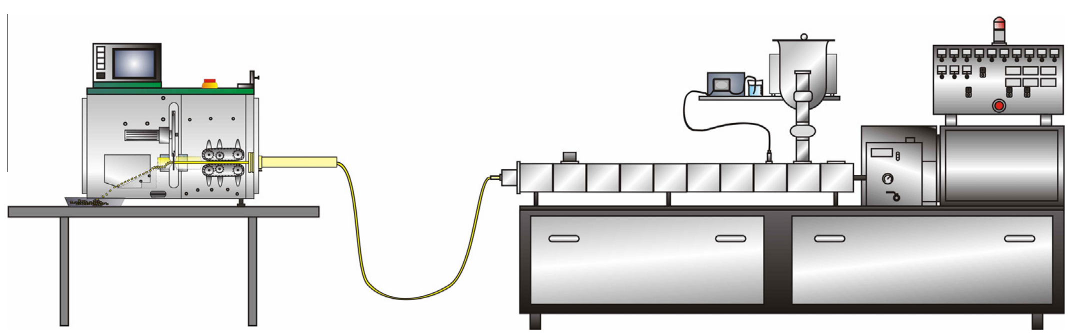

Fig. 1a. Schematic view of the production line; a co-rotating twin-screw extruder type ZSE 27 HP–PH from Leistritz (Nürnberg, Germany) is used for plasticizing the melt. The homogenous strand is processed by a rotary flying-knife cutting machine–type Dynamat 20 from Metzner (Neu-Ulm, Germany) to tablet like single dosed dosage forms. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

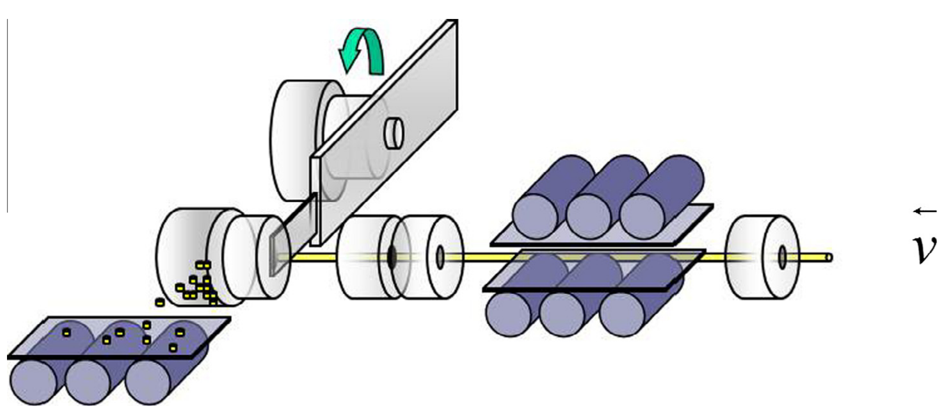

Fig. 1b. Schematic view of the cutting process; a rotary flying-knife cutter is used for cutting the strand. Conveyor belts are used for exact positioning of the strand. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)