Research and Reviews: Drug Delivery

Multi-Unit Particulate Systems for Rapid Formulation Development of New Chemical Entities

Abdul Khader Mohammad*

Department of Computer Science, Majmaah University, Al-Majmaah, Kingdom of Saudi Arabia

Mini Review

Received: 27-Aug-2022, Manuscript No. DD-22-73058; **Editor assigned:** 29-Aug-2022, PreQC No. DD-22-73058 (PQ); **Reviewed:** 12-Sep-2022, QC No. DD-22-73058; **Revised:** 10-Nov-2022, Manuscript No. DD-22-73058 (R); **Published:** 17-Nov-2022, DOI: 10.4172/DD.6.5.001

***For Correspondence :** Abdul Khader Mohammad, Department of Computer Science, Majmaah University, Al-Majmaah, Kingdom of Saudi Arabia;

Email: imran.bits@gmail.com

Keywords: Contract Manufacturing Organizations; Animal studies; Formulations; Croscarmellose sodium; Sodium starch glycolate

ABSTRACT

Drug product development of New Chemical Entities (NCE) is a critical aspect of bringing a new drug molecule to market. Time is of essence in NCE development programs and emphasis is placed on speed, in terms of product development and commercialization. For many NCE programs, the cost of Active Pharmaceutical Ingredient (API) and availability are a bottleneck and therefore creative ways are needed to make use of the limited API to advance drug product development. Multi unit particulate systems offer one such advantage in leveraging limited API for pharmaceutical developmental intended for clinical use. Current technologies, such as oral Multiparticulate Drug Delivery Systems (MDDS), have gained immensely in importance, not only because of their ability to control drug release, but also for the modified drug-release profiles they facilitate.

INTRODUCTION

In the development of New Chemical Entities (NCE), the quantities of drug substance available early on in development are limited. Solid oral dosage formulation development at lab scale using lab/pilot scale equipment requires API in the kilogram range. While this may be possible in some cases, in many cases the API availability early on in the program is in the gram range. Many Contract Manufacturing Organizations (CMO) lack the ability to develop solid oral dosage formulations with a sub kilogram amount of API. Innovative technologies can be leveraged in solving this problem [1]. These systems release the drug with constant or variable release rates, thus maintaining drug concentration within the therapeutic window for a prolonged period of time. The desired release profile facilitates controlled absorption through the target site in the body, ensures good therapeutic activity, and reduces side effects. MDDS comprises a large number of small discrete particles (i.e., active ingredient and excipients), each demonstrating desirable features. They are prepared by methods including extrusion spheronization, palletization, granulation, spray drying, and spray congealing.

One such technology is to use a bench top extruder spheronizer unit which includes the granulation, extrusion, and spherization units in one machine. The benchtop equipment can handle powders in the range of 10–20 g, for which only a few grams of API is needed depending on the drug load. Several formulations can be developed with less than 100 g of API and the formulations thus designed can be tested in animal studies to assess their *in vivo* absorption behavior. Based on the exposure data in animals, a few of the formulations can be rank ordered and developed at clinical scale for early testing in phase 1 studies and beyond [2].

Multiunit Particulate Systems (MUPS) are a novel MDDS technique for controlled and modified drug delivery. MUPS

offer various advantages over other systems, including reduced risk of local irritation and toxicity, predictable bioavailability, reduced likelihood of dose dumping, minimized fluctuations in plasma concentration of drug, and high dose-strength administration. Multiparticulate systems show more reproducible pharmacokinetic behavior and lower intra- and intersubject variability than conventional (*i.e.*, monolithic) formulations. Tableting of pellets reduces the esophageal residence time, compared with capsules, and improves physicochemical stability, compared with suspensions.

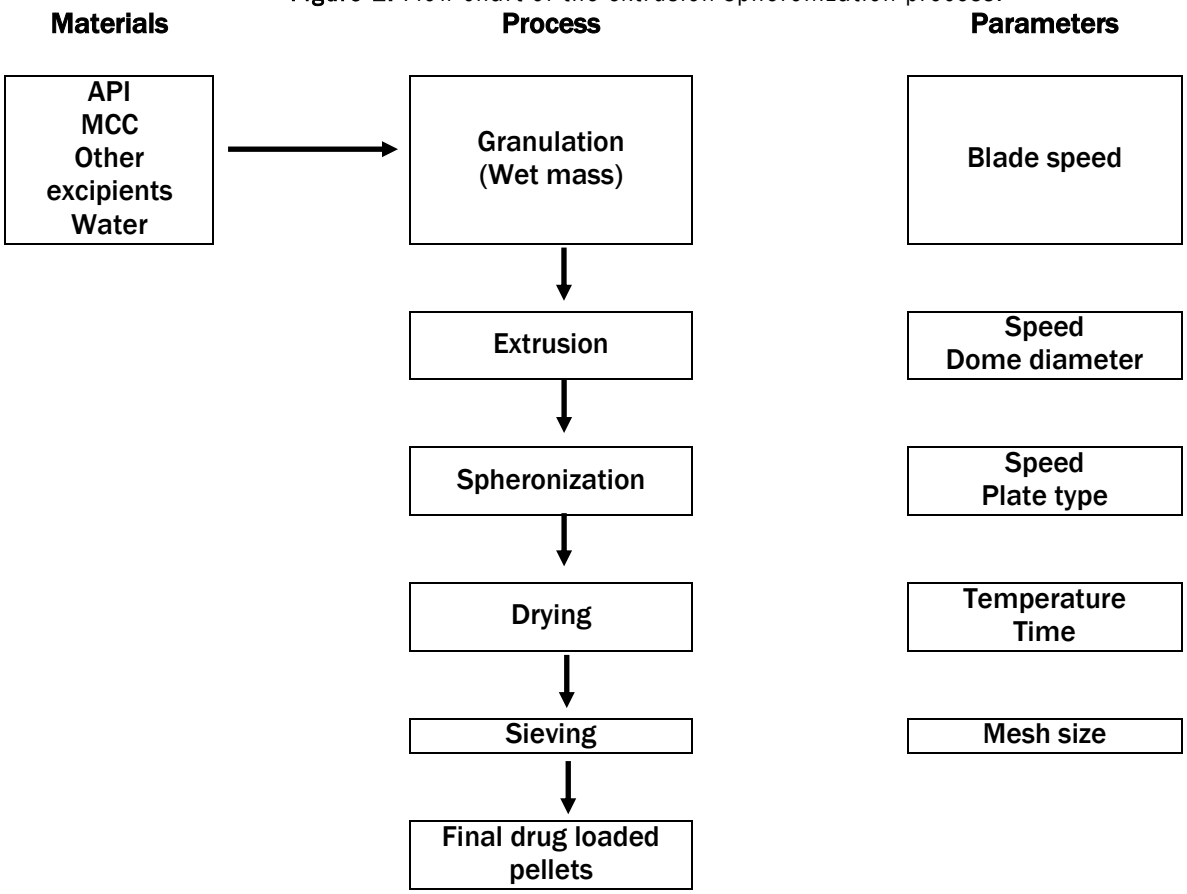
The applications for which MUPS formulations are developed include taste masking (*i.e.*, orodispersible MUPS tablets), enteric release (e.g., of acid-labile drugs), and modified- or controlled release orodispersible drugs for geriatric or pediatric patients. The technology of preparing compacted MUPS ensures that the desired objectives (e.g., taste masking coupled with orodispersibility as well as modified-release characteristics) are effectively achieved.

LITERATURE REVIEW

Rapid formulation development of drug loaded pellets for NCEs

Extrusion spheronization process: In a typical extrusion experiment, the components are few and therefore the development is less complicated compared to other pharmaceutical technologies. Micro Crystalline Cellulose (MCC) has been proven for its functionality as a pelletizing agent and is used in quantities ranging up to 90% w/w of the formulation on a case by case basis. Hydroxy Propyl Methyl Cellulose (HPMC) can also be used as a plasticizer that aids in the extrusion of the wet mass. HPMC can be typically used in concentrations of up to 5% w/w. Disintegrants such a croscarmellose sodium, sodium starch glycolate, crosspovidone etc. can be used in quantities of up to 5% w/w. Higher quantities of disintegrating agents can be utilized if need be. A binding agent is typically not necessary for pellet formation, however it can be used to address a particular need. A comprehensive flowchart of the extrusion spheronization process with parameters relevant to the benchtop unit is presented in (Figure 1).

Figure 1. Flow chart of the extrusion spheronization process.



Formulation optimization

A full or partial DOE design can be utilized by varying the quantities of each of the aforementioned excipients to

determine the optimum formula that meets all the critical quality attributes. In most cases, about 10 experiments are adequate in determining optimum formula that satisfies all the critical quality attributes. Assuming a high drug load of 50% w/w, this exercise would only need 50 grams of API at a batch size of 10 g [3].

Process optimization

From a process standpoint, several process parameters such as granulator blade velocity, extruder speed, spheronizer speed, and spheronizer plate type can be adjusted to obtain the desired product. The process can be studied either using a DOE approach or by modifying One Variable at a Time (OVAT). Since the process parameters from a benchtop machine cannot be directly translated to pilot scale equipment, a thorough study of process parameters on the benchtop equipment is not often necessary. A process that yields pellets of a narrow particle size distribution and near spherical shape is adequate for the purpose of early product development. Later in development, when the process is transferred to lab scale equipment with batch sizes in the kilogram range, the parameters will have to be determined on the formula developed using the benchtop machine [4].

Drying, storage, and characterization

The wet pellets obtained from the benchtop pelletizer can be dried in a lab scale oven. Usually, the drying process takes a few hours, and the end point can be easily achieved as measured by Loss on Drying (LOD). Typically, an LOD of less than 2% is achieved within a few hours and can be measured on the crushed pellets at the end of the pre determined drying time. The pellets can be crushed in a mortar. It is advisable to immediately test the crushed pellet for LOD as opposed to leaving them exposed for long periods of time, to avoid moisture uptake.

The dried pellets can be stored in plastic or glass vials with caps, and covered with aluminum foil or parafilm to ensure maximum protection. The dried pellets can be tested for assay, impurities, moisture content, dissolution etc. Additionally, scanning electron microscopy can be performed to understand the surface morphology of the pellets, light microscopy images can be taken to understand the sphericity in a qualitative manner. Some microscopes have the ability to measure the dimensions of the pellets and using this capability, sphericity can also be determined (the details of which are outside of the scope of this review). The characterized pellets can be tested in animal studies to determine their absorption *in vivo*.

Coating of pellets for functionality

Depending on availability of appropriate small scale equipment, the pellets can be coated with different polymers. A seal coat can be applied using polymers such as HPMC or Eudragit for moisture protection as well as for the creation of a smooth surface. In our experience, seal coating of about 5% was successful in controlling the degradation of API on long term storage. Coatings of ethyl cellulose, acrylate based polymers (Eudragit RS/RL), polyvinyl acetate etc. can be applied on the pellets. The polymer coated pellets can be analyzed for dissolution. Information on the approximate coating level needed for controlled release, or enteric release can also be obtained [5-10].

DISCUSSION

All activities mentioned in this article can be accomplished within a record time of less than 3 months. Given the need of speed to clinic, this general approach can be very beneficial in cases where API availability is low and the information of dose is unknown. This is a powerful tool which if applied properly, can have lasting results for the length of the product life cycle.

CONCLUSION

In summary, extrusion-spheronization using a bench top unit is a very powerful tool in developing solid oral dosage formulations with small quantities of API. The drug loaded pellets can be coated with different polymers depending on the attributes desired. While the process parameters may not be translated onto pilot scale equipment, the formulation information derived from the benchtop equipment can be translated as is into pilot scale equipment and for further scale-up. Furthermore, using this process, complex formulation with controlled release and enteric release functionality can be developed without the need for applying a polymeric coating, but this is not the focus of the current article and will be discussed separately.

REFERENCES

1. Abdul AS, et al. A flexible technology for modified release drugs: Multiple Unit Pellet System (MUPS). J Control Release. 2010;147:2–16.
2. Schwartz JB, et al. Compaction studies on beads: compression and consolidation parameters. Drug Dev Ind Pharm. 1994;20:3105–3129.
3. Johansson B, et al. Effect of pellet size on degree of deformation and densification during compression and on

compactability of microcrystalline cellulose pellets. Int J Pharm. 1998;163:35–48.
4. Millili GP, et al. The strength of microcrystalline cellulose pellets: The effect of granulating with water/ethanol mixtures. Drug Dev Ind Pharm. 1990;16:1411–1426.
5. Lehmann K, et al. Schnellzerfallende tablet ten met gesteuerter wirkstoffabgabe. Pharm Ind. 1993;55:940–947.
6. Sivalingan G, et al. Multiparticulate Drug Delivery System. Res J Pharm Technol. 2020;13:3501-3507.
7. Tran PH, et al. Controlled release systems containing solid dispersions: Strategies and mechanisms. Pharm Res. 2011;28:2353-2378.
8. Verma RK, et al. Drug delivery technologies and future directions. Pharm Technol. 2001;25:1-4.
9. Herrero M, et al. Green extraction processes, biorefineries and sustainability: Recovery of high added-value products from natural sources. J Supercrit Fluids. 2018;134:252-259.
10. O'Brien MN, et al. Challenges and opportunities in the development of complex generic long acting injectable drug products. J Control Release. 2021;336:144-158.