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REVIEW ARTICLE

Combating oral drug delivery challenges through innovations in pelletization

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ABSTRACT
The complex pathophysiology and chronic nature of the diseases pose several challenges in the treatment strategy. The evolution of drug delivery science from conventional to the novel has helped tremendously but, at the same time, made the drug delivery very expensive. Research in the area of pelletization is one solution to most of these challenges. The use of advanced and rational polymers combinations helped deliver the medication at the site minimizing the adverse reactions and helping in achieving maximum systemic drug concentration to elicit a pharmacological response. This review article highlights a few major breakthroughs in pelletization using extrusion spheronization and the hot-melt extrusion process with the use of novel polymers like pluronic, eudragits, etc. The wide arena of applications has helped in combating treatment challenges associated with chronic ailments
Keywords; *MUPS, Pulsatile delivery, Extrusion spheronization, Hot Melt extrusion, gastric emptying of pellets*

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INTRODUCTION

Conventional tablets and capsules are the most preferred dosage forms by the patients; however, the challenges of dose dumping and drug interactions in combination drug delivery associated made scientists look for alternate drug delivery (1). Multiunit particulate systems use the different drug pellets either compressed into a tablet or filled in a capsule, thereby increasing the stability. Pellets are discrete spherical particles that can be processed by the use of API and excipient together. The nature of excipients decides the process (2). The non-lipidic polymers are processed majorly through extrusion spheronization, whereas the lipidic excipients are processed by hot-melt extrusion (3). The pellets are prepared mainly in two forms, either matrix type or reservoir type. The matrix systems help in sustaining the release of the drug through the use of advanced polymers, whereas innovations in the coating of these systems achieve controlled release of the drug (4). A number of factors affect the development of pellets through either extrusion spheronization or hot-melt extrusion, as summarized in Figure 1.

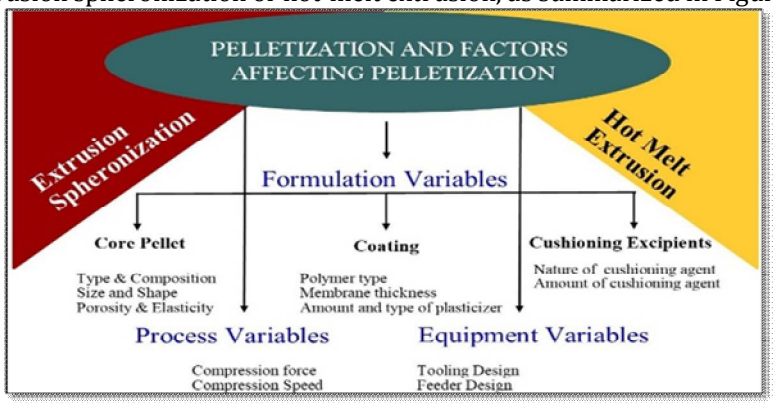

Figure 1: Factors affecting the pelletization process

GASTRIC EMPTYING OF PELLETS

The gastric emptying in the fed and fasting state varies, leading to changes in the absorption pattern of the drug and making it bioavailable. The small solid particles pass the pylorus sphincter through low amplitude contractions. In the fed state, gastric emptying of particle size of 0.7 mm is facilitated, whereas, in the fasting state, the particle size of 3.6 mm is emptied from the stomach (5). The researchers found that the drug (Didanosine) administered to fasted subjects absorbed faster from pellets compared to the tablet dosage form (6). However, in another study, it was observed that the tablets emptied from the stomach much faster (mean 0.55 hr) than pellets (0.81 hr) therefore presenting pellets as a convenient dosage form for the drug targeting stomach without leading to dose dumping. This favored reducing the gastric irritation to the gastric mucosa and the degradation of drugs (7). The other studies revealed that the pellets of the same size administered in the fed condition exhibited delayed gastric emptying compared to fasted condition(8). The pellets remained in the stomach till the next meal time, and that further prolonged their gastric emptying (9).

PELLETS PROCESSING IN EXTRUSION SPHERONIZATION

Pellets offer a multitude of advantages over granules when it is considered to be delivered through tablet. The irregularities in the shape and size of the granules is the biggest problem. The spherical shape of the pellets can be achieved by a combination of cellulosic material with lactose which is harder and more brittle as diluent. The use of only cellulosic material leads to the formation of strong and elastic pellets. These pellets reveal low connectivity between each other during compaction (10). The use of GMS, which is soft and ductile material, along with ethanol as a solvent, increase the porosity of pellets and gives uniformity in the sphericity of the pellets. The physical attributes of the pellets gained during the drying process adversely affect the compaction process. More porous pellets that can result due to increased drying rate lead to more deformable pellets. This may affect the prolonged release properties of pellets. The key attribute of the pellet looked at during compaction is its non-rupturable coating (11, 12).

The coating to pellets is applied to achieve high stability, to alter the release, mask the bitterness of API, improve elegance and to impart mechanical strength. Cellulosic polymers like Ethylcellulose, Hydroxy Propyl Methyl Cellulose (HPMC), HPMC Phthalates, Sodium Carboxy Methyl Cellulose, and Ethoxy Propyl Cellulose are used routinely; however, the innovation in polymers science brought into the picture the acrylic polymers with superior properties. The commonly used acrylic polymers are Eudragit® or Kollicoat® (13). The mechanical strength of the cellulosic pellets is generally strengthened using plasticizers. Usually, 10% Aquacoat® or Surelease® coating on the pellets is sufficient to render good tensile strength higher than other coated pellets. Scientists developed disintegrating tablets releasing less than 10%w/w of the active ingredient within two h in 0.1 MHCl from enteric-coated ASA or indomethacin pellets coated with Eudragit® L (14, 15).

The pellets coated with Eudragit® RL30D, RS30D and NE30D revealed excellent sustained-release properties and were found suitable to be compressed into fast disintegrating tablets. According to Wagner et al. (16), using Eudragit® FS30D at a high coating level reduced damage to the particle coatings in the tablet. It may be concluded that enteric coatings with adequate mechanical stability and appropriate flexibility can be created by combining Eudragit® FS30D with Eudragit® L30D55. However, Gupta et al. showed that utilizing Eudragit® L30D55 at 35% and propylene glycol at 20% as a plasticizer, enteric-coated pellets could be compressed into tablets without considerable damage (17).

Because of the low minimum film formation temperature, Kollicoat® SR30D coated pellets rarely require a plasticizer or a curing phase (thermal after-treatment). The pellets are also easy to manufacture and feature a pH-independent drug release. Plasticizer-free Kollicoat® SR coatings were too brittle and ruptured as the coated pellets were unable to withstand compression. The addition of a plasticizer (10 percent w/w triethyl citrate (TEC) greatly increased the flexibility of the coatings. Because of the increased mechanical qualities, adding merely 10% TEC to Kollicoat® SR30D resulted in nearly unchanged drug release patterns at various compression forces (18).

A number of excipients are used with pellets during compression to protect the rupture and damage of the pellets by forming a cushioning layer around the pellet. The selection of excipients should be such that it should form a rapidly disintegrating hard tablet at low compression force. Bekapress D2, a brittle excipient when compared with Avicel PH 200 and PEG 6000 for compression of eudragit coated bisacodyl pellets, resulted in maximum damage to the pellets. The other studies showed a combination of 25% PEG 3350, 50% MCC, and 25% crospovidone was most suitable for minimizing compression force damage to the coating of pellets; however, this combination decreased the release rate of the theophylline from the tablet (19).

The researchers even studied soft materials like PEG, GMS and glyceryl behenate for cushioning effect to hard pellets of MCC. The MCC fibress were able to adsorb 15-20 % of soft material and did not show any impact on the pellet formation (20).
Debunne et al processed piroxicam pellets and subsequently studied the effect of disintegrants on the disintegration behavior of tablets. Kollidon CL resulted in timely disintegration in 0.1 N HCl (within 15 min) as compared to sodium croscarmellose (Ac–Di–Sol), sodium carboxymethyl starch (Explotab) which took more than 1 hr to disintegrate the compressed tablet of piroxicam pellets (21) .

PELLETS PROCESSING IN HOT MELT EXTRUSION

Uniform molecular dispersion, which is organic solvent-free, can be efficiently processed through hot-melt extrusion. The wet mass-produced with altered and modified-release properties by the use of various excipients can subsequently be spheronised (22).
Young et al., 2003 compared the pellets prepared by conventional extrusion spheronization and hot melt extrusion spheronization technique. A mixture of MCC, Eudragit 4135F, and PEG 8000 along with theophylline, was used in the study. A narrow particle size distribution and controlled dissolution were obtained with pellets prepared from the hot-melt extruded mass (23). A biphasic release profile was obtained wherein a slow controlled release followed by fast release was obtained in diltiazem pellets processed by hot-melt extrusion using ethylcellulose, cellulose acetate butyrate, poly(ethylene-co-vinyl acetate), and a polymethacrylate derivative (Eudragit® RSPM) (24)..
A study showed that Pellets with a very narrow particle size distribution, high mechanical stability, and low porosity could be processed by the use of different starch of natural origin. The crucial part of starch-based hot-melt extruded pellets is that the pellets erode completely due to high porosity (25). Plasticizers used in the process play an important role in controlling the release. Glyceryl monostearate (GMS) and tributyl citrate (TBC) was used to increase the drug release without impacting the processing parameters (26). The small extended release pellets were prepared for parenteral purposes using high molecular weight polyethylene oxide (PEO) and gelling agents (xanthan gum, guar gum, and gellan gum) (27).

MULTIPARTICULATE FORMULATION APPROACH

Reservoir systems with rupturable polymeric coatings:

The majority of multiparticulate pulsatile delivery systems are reservoirs with a rupturable polymeric layer on top. Due to pressure build-up within the system, medication is released from the core when water penetration causes rupturing of the surrounding polymer layer. Swelling agents, gas-producing effervescent excipients, or enhanced osmotic pressure can all be used to achieve the pressure required to rupture the coating. The lag time is influenced by water permeability and the outer membrane's mechanical resistance. Water-soluble medications are released primarily by diffusion, whereas water-insoluble pharmaceuticals are released primarily through dissolution. Time-controlled explosion systems (TES) were found by Ueda et al (28) , in which the medication is delivered via a novel mechanism that is neither diffusion control nor dissolution control but rather an explosion of the outer membrane. This method is particularly beneficial with water-insoluble medicines, while prior art delay mechanisms based on drug diffusion via a permeable coating would be ineffective. Both single and multiple-unit dosage formulations were generated using TES. A core in both situations contains the medicine, as well as an inert osmotic agent and appropriate disintegrants. Individual units can be covered with a protective layer and subsequently with a semi-permeable layer, which controls the rate of water influx into the osmotic core. Due to an increase in osmotic pressure caused by water infiltration, the core eventually explodes, releasing the medication immediately. Swelling agents can also be used to create an explosion in the formulation. Different release patterns can be achieved by changing the form of TES; for example, in the form of a tablet, the drug is released quickly after the outer membrane explodes, whereas in the form of beads or granules, the drug is released with a zero-order pattern after a definite lag time due to the time variance of the outer membrane explosion in each bead or granule. The rupturing of the exterior water-insoluble barrier generated by the explosive swelling impact of swelling agents controls drug release over time. With increasing coating levels and higher concentrations of talc or lipophilic plasticizer in the coating, the lag time increased. The drug was stacked on an inner core (polystyrene balls or non-pareil sucrose beads), followed by a swellable layer (e.g., hydroxypropyl cellulose), and an insoluble polymeric top layer in a four-layered time-controlled explosion system (e.g., ethylcellulose) (29). This technique was used to conduct an in vivo trial in conscious dogs for a novel vasodilator medication called FK409. FK409 was detected in the blood after 3 hours, and the maximum level was reached after 5 hours, which was consistent with the in vitro release profile. In human bioavailability tests, a 3-hour lag time was observed, with a 5-hour latency to peak concentration. These trials demonstrate the system's suitability for treating

disorders with nocturnal symptoms (30). The release from TES devices was reported as complete, regardless of the pH of the environment or the solubility of the medication. The incorporation of a water-soluble polymer in the insoluble polymeric membrane of the TES has been suggested as a way to improve control over the release pattern. This water-soluble polymer is an enteric coating polymer, which means it only becomes soluble at pH levels above a specified threshold. This keeps the polymer from dissolving in the stomach. When the pellet reaches the intestine's elevated pH, the polymer dissolves and weakens the membrane coating, allowing the weakened membrane to explode after a predetermined amount of time in the intestinal environment. Water impermeable materials can be incorporated into coatings to increase the lag time of TES systems. The rate of swelling can be slowed and the time to explosion can be extended and regulated by slowing the influx of water into the inside of the pellet holding the swelling agent.

Reservoir systems with soluble or eroding polymer coatings

Another sort of multiparticulate pulsatile system that uses soluble/erodible layers instead of rupturable coatings is the reservoir-type multiparticulate pulsatile system. After a certain amount of time has passed, the barrier melts or erodes, allowing medication to burst out of the reservoir core. In general, the thickness of the coating layer can regulate the lag time before drug release in these types of devices. However, because the release mechanism in these systems is dissolving, a larger ratio of drug solubility to dosage amount is required for rapid drug release after the lag period. In an attempt to transport medications to diverse places in the gastrointestinal (GI) tract, the lag periods delayed by hydration of various thicknesses of Eudragit RS films were investigated [29]. Diltiazem hydrochloride was chosen as a model medicine because of its excellent water solubility, which is pH-independent. The lag time could be varied in a theoretical simulation by adjusting the thickness of the coated polymer, which was proportional to the amount of dry polymer in the coating. The lag time and the square of the amount of polymer-coated, as well as the release rate at steady-state and the inverse of the amount of polymer-coated, were both accurately anticipated. Coatings that are pH-sensitive have traditionally been used because they have a considerable increase in solubility at a certain point in the GI tract. This sensitivity has been used to block stomach release, allowing for total intestinal release (31). A pH-sensitive multi-particulate system based on Eudragit S-100 coated pellets was developed for the delivery of diltiazem hydrochloride for the treatment of angina pectoris (32). Aqueous extrusion spheronization was used to make the drug-loaded pellets, with microcrystalline cellulose as a spheronizing aid and PVP K 30 as a binder. To make the pH sensitive pellets, different coat weights of Eudragit S-100 were applied to the drug-loaded pellets. The drug release was found to be dependent on the coat weights applied and the pH of the dissolution fluid in vitro dissolving tests of coated pellets using the pH progression method. A single dose form that may release its components at various times and locations throughout the gastrointestinal tract could be a highly effective technique.

Floating multiparticulate pulsatile systems

The above-mentioned conventional multiparticulate pulsatile release dosage forms have a prolonged residence time in the gastrointestinal system, which may result in in vivo variability and bioavailability issues due to the extremely variable nature of the gastric emptying process. Low density floating multiparticulate pulsatile dose forms, on the other hand, are only found in the stomach and are unaffected by changes in pH, local environment, or gastric emptying rate. These dose forms are also ideal for medications that are absorbed via the stomach or that require local administration in the stomach. As a result of these concerns, multiparticulate pulsatile release dosage forms with stomach retention characteristics were developed. For time and site-specific medication release of meloxicam for chronopharmacotherapy of rheumatoid arthritis, a multiparticulate floating-pulsatile drug delivery system was created employing porous calcium silicate (Fluorite RE) and sodium alginate (33). By rapidly evaporating the solvent from a medicinal solution containing scattered FLR, meloxicam was adsorbed on the Flourite RE (FLR). Using 3(2) factorial designs, drug-adsorbed FLR powder was used to create calcium alginate beads using the ionotropic gelation process. The density of beads and the hydrophobicity of the medication were used to adjust the floating time in this system. Because of the ease with which the desired drug delivery system and drug release profile may be achieved by cross-linking control, the insolubility of crosslinked beads in the gastric environment, and broad regulatory acceptability, polysaccharides are commonly utilised in oral drug delivery systems.

Mucoadhesive pellets

The content of the investigation was to develop and optimize buccal hot-melt extruded (HME) pellets for Pioglitazone (PIO) and Felodipine (FDP) in combined dosage form for the management of diabetes and hypertension using Box–Behnken design. In this study, three factors were evaluated at three levels. Amount of PEON80 (A1), amount of HPMCK4M (A2) and amount of plasticizer (A3) as independent

variables and bioadhesion strength (BS) (B1), erosion (B2) and percent drug release in 1 h Q1 (B3) as responses. Pellets were prepared by the hot-melt extrusion technique. HME pellets were evaluated for compatibility, physicochemical properties, ex vivo permeation, in vivo bioavailability in pigs, and stability studies. Pellets demonstrated no drug excipient interaction and excellent content uniformity. Statistically optimized HME pellet showed BS of 2.92 ± 0.04 N, erosion of 10.5 ± 2.05% and percent drug release of 31.9 ± 2.1% and 29.2 ± 1.9% for PIO and FDP respectively. Statistically optimized pellet prolonged in vitro drug release of 96.6% PIO and 94.5% FDP release in 6 h and permeated 68.6 and 66.4% with flux of 0.372 and 0.361 mg h−1 cm−2 of PIO and FDP, respectively through the porcine buccal membrane. Statistically significant ($p < 0.01$) improvement in bioavailability was observed for PIO (1.9-folds) and FDP (2.1-folds). No significant changes were observed in 6 months during stability studies (34).

PULSATILE DRUG DELIVERY:

Advances in research aimed at underlying concepts to offer both commercial and therapeutic values to health care goods have contributed to novel drug delivery systems over the last three decades. These novel and/or better delivery methods function on a variety of concepts, supplying variable/constant medication doses throughout a specific time period in our bodies, based on the notion that physiologic parameters are consistent over time (35, 36) . However, a new concept known as chronotherapy has been proposed to debunk this common belief. Chronotherapeutics is a clinical approach that involves coordinating medicine delivery with the body's circadian rhythm, including disease states, in order to maximize health benefits while minimizing side effects. Several diseases and physiological functions are known to be dependent on circadian rhythm. Numerous studies have found that synchronizing medication to the biological rhythm can improve pharmacokinetics, therapeutic efficacy, and side effects. A significant component in achieving maximum pharmacological impact is specificity in delivering increased amounts of the drug in a burst at circadian timings connected with certain clinical disorders (29). In disorders such as bronchial asthma, myocardial infarction, angina pectoris, rheumatic disease, ulcer, diabetes, attention deficit syndrome, hypercholesterolemia, and hypertension, specific rhythms in the onset and degree of symptoms have been documented. All of this pushed for the creation of "Pulsatile Drug Delivery Systems." In these systems, a predetermined amount of drug molecules is released rapidly and transiently within a short time period after a predetermined off-release period (37). Pulsatile delivery can be accomplished using a variety of approaches, which are broadly classed as Single-unit and Multiple-unit systems. They all act on the same basic principles of erosion or dissolving, swelling and rupturing, and a system based on membrane permeability changes. However, inadvertent disintegration of the formulation due to manufacturing deficiencies or atypical gastric physiology may result in substantially reduced systemic drug bioavailability or loss of local therapeutic efficacy in single-unit pulsatile drug delivery systems. Multiparticulate dose forms are increasingly being preferred over single-unit dosage forms in current pharmaceutical applications involving pulsatile delivery. Increased bioavailability, predictable, reproducible, and generally short gastric residence time; less chance of dose dumping; reduced risk of local irritation; and the freedom to blend pellets with different compositions or release patterns are among the potential benefits. These systems can readily travel through the GI tract due to their smaller particle size, resulting in less inter-and intra-subject variability. However, because of the correspondingly larger need for excipients, the potential drug loading of a multiparticulate system is reduced (e.g., sugar cores). Despite the fact that numerous technologies for the manufacturing of microparticulate systems have been developed, spray-drying, spheronization, and film-coating technology remain the most common. True reservoir devices have yet to succeed due to limitations in process variables induced by several formulation processes, which can operate as technical impediments in manufacturing reproducibility, as well as a lack of safety and efficacy (38).

CONCLUSION

The difficulties of turning pellets into tablets are obvious. Pellets are compacted differently than powdered excipients, and the mechanical properties of the resulting compacts are considerably different. To generate pellet-containing tablets with the same features, including drug release properties, several materials, and process-related parameters must be tuned. The type of polymer chosen for pellet coating is the most crucial variable. The tensile performance of the polymeric coating, as well as its response to various types of stresses, must be researched in order to choose the best polymer to coat the compressed pellets. To avoid coating rupture, the formulation of the pellet core and final tableting excipients must be carefully chosen. The pellet–excipient ratio and the compression forces are important variables. Excipients employed, size and porosity of the pellet core, and the kind and amount of protecting excipients are all relevant formulation factors influencing the compression behavior of pellet-containing

tablets. The wide arena of applications has helped in combating treatment challenges associated with chronic ailments.

REFERENCES

1. Gaber DM, Nafee N, Abdallah OY. (2015). Mini-tablets versus pellets as promising multiparticulate modified release delivery systems for highly soluble drugs. Int J Pharm. 488(1-2):86-94.
2. Breitkreutz J, Boos J. (2011). Drug delivery and formulations. Handb Exp Pharmacol. 205:91-107.
3. Bhairav BA, Kokane PA, Saudagar RB. (2016). Hot Melt Extrusion Technique-A Review. Research Journal of Science and Technology. ;8(3):155-62.
4. Vergote G, Vervaet C, Van Driessche I, Hoste S, De Smedt S, Demeester J, et al. (2001). An oral controlled release matrix pellet formulation containing nanocrystalline ketoprofen. International Journal of Pharmaceutics. ;219(1-2):81-7.
5. Huang Y, Huang Z, Wu M, Liu Y, Ma C, Zhang X, et al. (2019). Modified-release oral pellets for duodenum delivery of doxycycline hyclate. Drug Dev Res. ;80(7):958-69.
6. Damle BD, Yan JH, Behr D, O'Mara E, Nichola P, Kaul S, et al. (2002). Effect of food on the oral bioavailability of didanosine from encapsulated enteric-coated beads. The Journal of Clinical Pharmacology.;42(4):419-27.
7. Choe SY, Neudeck BL, Welage LS, Amidon GE, Barnett JL, Amidon GL. (2001). Novel method to assess gastric emptying in humans: the Pellet Gastric Emptying Test. European journal of pharmaceutical sciences. ;14(4):347-53.
8. Saphier S, Rosner A, Brandeis R, Karton Y. (2010). Gastro intestinal tracking and gastric emptying of solid dosage forms in rats using X-ray imagining. International journal of pharmaceutics.;388(1-2):190-5.
9. Newton JM. (2010). Gastric emptying of multi-particulate dosage forms. International journal of pharmaceutics. ;395(1-2):2-8.
10. Goyanes A, Martínez-Pacheco R. (2015). New co-processed MCC-based excipient for fast release of low solubility drugs from pellets prepared by extrusion-spheronization. Drug development and industrial pharmacy.;41(3):362-8.
11. Khatri P, Desai D, Shelke N, Minko T. (2018). Role of plasticizer in membrane coated extended release oral drug delivery system. Journal of Drug Delivery Science and Technology.44:231-43.
12. Lecomte F, Siepmann J, Walther M, MacRae R, Bodmeier R. (2004). Polymer blends used for the aqueous coating of solid dosage forms: importance of the type of plasticizer. Journal of Controlled Release. 99(1):1-13.
13. Wang C-C, Zhang G, H. Shah N, Infeld MH, Waseem Malick A, McGinity JW. (1997). Influence of plasticizers on the mechanical properties of pellets containing Eudragit® RS 30 D. International Journal of Pharmaceutics.;152(2):153-63.
14. Samir AlKhatib H, Sakr A. (2003). Optimization of Methacrylic Acid Ester Copolymers Blends as Controlled Release Coatings Using Response Surface Methodology. Pharmaceutical Development and Technology ;8(1):87-96.
15. Shahdadi Sardo H, Saremnejad F, Bagheri S, Akhgari A, Afrasiabi Garekani H, Sadeghi F. (2019). A review on 5-aminosalicylic acid colon-targeted oral drug delivery systems. Int J Pharm. ;558:367-79.
16. Wagner KG, Krumme M, Schmidt PC.(1994). Investigation of the pellet-distribution in single tablets via image analysis. European journal of pharmaceutics and biopharmaceutics.;47(1):79-85.
17. Gupta VK, Beckert TE, Price JC. (2001). A novel pH-and time-based multi-unit potential colonic drug delivery system. I. Development. International Journal of Pharmaceutics. 213(1-2):83-91.
18. Bürki KE. (2016). Preparation of taste masked orally disintegrating tablets by compression of coated pellets.
19. Abdul S, Chandewar AV, Jaiswal SB. (2010). A flexible technology for modified-release drugs: multiple-unit pellet system (MUPS). Journal of controlled release. 147(1):2-16.
20. Rhee Y-S, Lee J-H, Lee B-J, Park E-S. (2010). Controlled-release pelletized dosage forms using the extrusion-spheronization process. Journal of Pharmaceutical Investigation. 40(spc):103-12.
21. Debunne A, Vervaet C, Remon JP.(2002). Development and in vitro evaluation of an enteric-coated multiparticulate drug delivery system for the administration of piroxicam to dogs. Eur J Pharm Biopharm.;54(3):343-8.
22. Augsburger LL, Hoag SW. (2008). Unit Operations and Mechanical Properties: Informa Healthcare USA.
23. Young C, Koleng J, McGinity J. (2003). Properties of drug-containing spherical pellets produced by a hot-melt extrusion and spheronization process. Journal of microencapsulation. 20(5):613-25.
24. Follonier N, Doelker E, Cole ET. (1994). Evaluation of hot-melt extrusion as a new technique for the production of polymer-based pellets for sustained release capsules containing high loadings of freely soluble drugs. Drug Development and Industrial Pharmacy. 20(8):1323-39.
25. Bialleck S, Rein H. (2011). Preparation of starch-based pellets by hot-melt extrusion. European Journal of Pharmaceutics and Biopharmaceutics. 79(2):440-8.
26. Roblegg E, Jäger E, Hodzic A, Koscher G, Mohr S, Zimmer A, et al. (2011). Development of sustained-release lipophilic calcium stearate pellets via hot melt extrusion. European Journal of Pharmaceutics and Biopharmaceutics. ;79(3):635-45.
27. Butreddy A, Sarabu S, Dumpa N, Bandari S, Repka MA. (2020). Extended release pellets prepared by hot melt extrusion technique for abuse deterrent potential: Category-1 in-vitro evaluation. Int J Pharm. ;587:119624.

28. Ueda Y, Hata T, Yamaguchi H, Ueda S, Kodani M.(1989). Time-controlled explosion systems and processes for preparing the same. Google Patents.
29. Roy P, Shahiwala A. (2009). Multiparticulate formulation approach to pulsatile drug delivery: current perspectives. Journal of controlled release. 134(2):74-80.
30. Hata T, Shimazaki Y, Kagayama A, Tamura S, Ueda S. (1994). Development of a novel drug delivery system, time-controlled explosion system (TES): V. Animal pharmacodynamic study and human bioavailability study. International journal of pharmaceutics.;110(1):1-7.
31. Nokhodchi A, Asare-Addo K. (2014). Drug release from matrix tablets: physiological parameters and the effect of food. Expert opinion on drug delivery. 11(9):1401-18.
32. Zhang L, Sang Y, Feng J, Li Z, Zhao A. (2016). Polysaccharide-based micro/nanocarriers for oral colon-targeted drug delivery. Journal of drug targeting. 24(7):579-89.
33. Ray S, Seth S. (2021). Modified biopolymer-based chronotherapeutic drug-delivery systems. Tailor-Made and Functionalized Biopolymer Systems: Elsevier; p. 613-34.
34. Palem CR, Dudhipala N, Battu SK, Goda S, Repka MA, Yamsani MR. (2015). Combined dosage form of pioglitazone and felodipine as mucoadhesive pellets via hot melt extrusion for improved buccal delivery with application of quality by design approach. Journal of Drug Delivery Science and Technology. 30:209-19.
35. Allen L, Ansel HC. (2013). Ansel's pharmaceutical dosage forms and drug delivery systems: Lippincott Williams & Wilkins.
36. Agrawal S, Fernandes J, Shaikh F, Patel V.(2022). Quality aspects in the development of pelletized dosage forms. Heliyon. :e08956.
37. Bussemer T, Otto I, Bodmeier R. (2001). Pulsatile drug-delivery systems. Critical Reviews™ in Therapeutic Drug Carrier Systems. 18(5).01-11
38. Battu S, Yalavarthi PR, Gopireddy VSR, Vattikuti UMR, Devi J, Vadlamudi HC. (2017). Chronopharmacokinetic Evaluation of Budesonide Multiparticulate Systems. Recent Pat Drug Deliv Formul. 11(3):221-9.