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Review

Hot melt extrusion: An industrially feasible approach for casting orodispersible film

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ABSTRACT

Over the recent few decades, many groups of formulation scientists are concentrating on rapid release dosage forms in oral cavity. Among all fast release dosage forms, orodispersible films are successful to attract pharmaceutical industry due to ease of formulation and extension patent life. Films are popular in patients too because of quick onset and user friendliness of dosage form. From the beginning, solvent casting has been selected as method of choice for manufacturing of orodispersible films. Solvent casting has been proved as a benchmark technology because of ease in product development, process optimization, process validation and technology transfer to production scale despite of some drawbacks like more number of unit operations involved and consumption of large quantity of solvents with controlled limits of organic volatile impurities in final formulation. The application of hot-melt extrusion (HME) in the pharmaceutical industry is consecutively increasing due to its proven innumerable advantages like solvent free continuous process with fewer unit operations and better content uniformity. Very few development activities has been initiated in the field of hot melt extruded orodispersible films so far. This extensive review covers detailed discussion of heavy duty industrial extruders, selection of downstream equipments, selection of excipients, common problems found in formulations and their remedies. Successive part of review addresses identification of critical quality attributes, quality target profile of product, criticality in selection of process parameters and material for substantial simulation in laboratory scale and production for successful technology transfer.

1. Introduction

The oral route is most preferred route of administration for drug delivery due to the aspect of patient compliance [1]. Nowadays, research and development activities on new active pharmaceutical ingredients (API) are remarkably less compared to new dosage form development of already existing molecules. New dosage form development of previously

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approved API with satisfactory regulatory acceptance is itself a challenge for formulation scientist [2]. Among the pharmaceutical dosage forms, the conventional tablet seems to be most popular. However, for the elderly and the infants, conventional tablet presents some difficulties for swallowing while liquid dosage forms are preferred [3]. Looking to the development history of oral solid, it can be said that drawback of one dosage form has been worked as a seed for implanting new dosage form. Chewable tablets have been accepted to those who cannot swallow tablets easily but the disadvantage of chewable tablet was the chalky taste, gritty particles and unpleasant taste of active [4–6]. Dispersible tablets and effervescent tablets, which were predissolved in a glass of water before consumption, solved some of these issues but use of insoluble lubricants resulted in a "scum" or dirty insoluble residue floating on the surface of the solution or on the sides of the container created patient discomfort [7].

To combine the advantages of tablets and liquids, the research activities has been focused on developing orodispersible tablets (ODTs) which are solid dosage forms that disintegrate rapidly in oral cavity within 1 min with improved ease of administration for patients who are mentally ill, disabled, uncooperative, pediatric and geriatric population [8,9]. Freeze-drying, sublimation, cotton candy, melt granulation, molding, phase-transition, spray-drying and effervescent technology are some of the widely accepted techniques for preparation of ODTs [10,11]. ODTs have been proved as a successful dosage form more than three decades. Cardinal Health's R.P. Scherer Corporation has patented Zydis technology which has been in commercial production since 1986 [12–14]. Other fast-dissolving oral technologies have been introduced last few decades, such as Lyoc, Orasolv, WOWTAB and Flashtab [15,16]. Despite of commercial success, there are some drawbacks of ODTs like hygroscopicity, friability and unpleasant taste of active. Hence, they need protection from moisture and ODTs are very brittle in nature which calls for specialized product packaging [17]. Since these tablets dissolve directly in the mouth, taste masking of bitter active is also an important factor [18,19]. The drawbacks of ODT have evolved the era of oral wafers or oral strip technology. Oral strip technology is mainly categorized in two parts, mucoadhesive films and flash release wafers [20].

1.1. *Mucoadhesive films*

Mucoadhesive film is applied to buccal and gingival mucosa and sticks to mucosal surface. Carbomers 974P and 971P are most widely used polymers for bioadhesion purpose. Mucoadhesive films are generally prepared by the methods such as hot melt extrusion and solvent casting [21,22]. As per the function and disintegration time, mucoadhesive films are categorized in two parts. (A) *Mucoadhesive melt away strip*: It sticks to the mucosa; totally dissolve within few minutes and continuously release the drug over time. Melt away films are prepared as monolayer films. (B) *Mucoadhesive sustained release film*: This type of wafer sticks to mucosa and remain there for up to several hours. For that duration, drug release is sustained and wafer must be removed at the termination of medication [23,24]. Oramoist is a sustained release oral wafer that adheres to the roof of mouth and enhances salivary secretion to prevent dry mouth syndrome (xerostomia) [25]. Sustained release films are prepared as monolayer as well as multilayer multiparticulate containing films [26–28].

1.2. *Flash release wafers*

Flash release wafers dissolve in maximum of 60 s and immediately release the drug in oral cavity. As per the site of application, the flash release wafers are categorized in two parts. (A) *Orodispersible film* (*ODF*): The ODF is ultrathin strip, which is similar to postage stamp in shape and size, with actives and mostly water soluble excipients like film forming polymers and plasticizers. The orodispersible films (ODFs) have larger surface area compared to ODTs that leads to rapid disintegration in oral cavity. Unlike the ODTs which are fragile and brittle, ODFs are flexible enough with adequate ease of transport and handling. Unlike the other liquid dosage forms, precise dosing and unit dose formulation is possible with ODFs. ODFs provide ease of swallowing and patient can take it without need of water. So, patients with dysphagia, repeated emesis, motion sickness and mental disorders can take it easily. ODF is commercially successful dosage form [29]. Under the brand name of Triaminic thin strips, Novartis has developed many combination therapies for long acting cough, cough with runny nose and cold with stuffy nose [30]. Listrine pocket pouches, launched by Pfizer, have proved ODF as commercially successful dosage form [31]. Kwang Dong formulated Sedera-ondansetron 50 mg loaded ODF in South Korea with appreciable taste masking of highly bitter active with maximum drug loading which is itself a big challenge to formulation scientists [32]. (B) *Sublingual films*: Formulation of these types of films is same as ODFs but the films are placed under a tongue rather than in oral cavity. Reckitt Benckiser pharma formulated Suboxone-buprenorphine and naloxone sublingual films which are used for maintenance treatment of opoid dependence [33].

Solvent casting is widely accepted for formulating flash release formulations [34]. In this technique, water soluble polymers, active and plasticizer are dissolved in water or other solvent; finally casted and dried in tray dryer [35–37]. Still there are some problems associated with solvent casting like number of unit operations involved and consumption of organic solvents with controlled limits of organic volatile impurities in final formulation. Field of hot melt extruded ODFs has been remained untouched till now. Hot melt extrusion is a continuous process without solvent and provides better content uniformity with fewer unit operations [29]. Successive part of this review article explores the hot melt technology as scientist-friendly and commercially viable technique with considerable emphasis on scale up model as well as formulation development as per quality by design approach.

2. Hot melt extrusion equipments used in orodispersible film formulation

Pharmaceutical-class extruders have evolved and adapted to mix drugs with carriers for various solid dosage forms. As per the requirement of dosage form, minor changes in configuration are adopted. In this section, different part of extruders has been discussed with special emphasis on ODF formulation.

2.1. Types of extruders

2.1.1. Ram extruder

Ram extruder operates with a positive displacement ram capable of generating high pressures to push molten materials through the die. Ram extruders are generally not preferred in ODF preparation by HME due to its low temperature uniformity and improper mixing abilities [38].

2.1.2. Screw extruder

Screw extruders are most widely accepted for pharmaceutical industry. Screw extruder consists of a rotating screw inside a heated barrel. Unlike ram extruder, a screw extruder provides more shear stress and intense mixing [38]. In pharmaceutical industry, two types of screw extruders are widely used as per requirement of product. (A) *Single screw extruder*: One screw rotates inside the barrel and is used for feeding, melting, devolatilizing and pumping. Intense mixing is not achieved with single screw extruder [38]. (B) *Twin screw extruder*: Twin screw extruders utilize two screws inside the heated barrel. Twin screw extruders have several advantages over single screw extruders, such as easier material feeding, high kneading and dispersing capacities; less tendency to overheat and shorter transit time [39]. Twin screw extruders are further classified as per their installation and working mechanism of screw. One is co-rotating and another is counter-rotating design. In co-rotating extruder designs, screw rotates in same direction and they can be operated at high screw speeds and achieve high outputs, while maintaining good mixing and conveying characteristics. In counter-rotating extruders, screw rotates in opposite direction. The counter-rotating designs are utilized when very high shear regions are needed as they subject materials to very high shear forces. Generally, it suffers from disadvantages of potential air entrapment, high-pressure generation and low maximum screw speeds and output [40]. Basic structural difference of different variants of screw extruders is shown in Fig. 1.

2.2. Parts of extruders

At a minimum, a screw extruder consists of three distinct parts like (a) conveying system for material transport and mixing (rotating screw, feed hopper and a temperature controlled barrel), (b) gear pump to eliminate inevitable small fluctuation in process, (c) die system for forming different shapes, (d) downstream auxiliary equipment for cooling, cutting or collecting the finished goods. Additionally, commercial grade systems include mass flow feeders to accurately meter materials into the feed hopper, process analytical technology to measure extrudate properties (near infra red systems and laser systems), liquid and solid side stuffers, and vacuum pumps to devolatize extrudates or film ribbons, roll collectors and calendaring equipment [41–44].

2.2.1. Screw element

The screws are the heart of any screw extruder and the design directly impacts the quality of the dosage form. Screw elements are flighted (threaded) for material transport, and nonflighted to create shear regions for melting or mixing. Screw designs can be shear-intensive and/or shear-passive according to required mechanism of mixing [38,42].

2.2.2. Barrel

Barrels for screw extruders can be either one-piece or modular and can be configured for downstream feeding like side stuffing and venting. Barrel sections are heated by electric heaters. Barrel heating and cooling facilitates a temperature set point to maintain the desired melt viscosity within the process section. Temperatures throughout the process are normally controlled by electrical heating bands and monitored by thermocouples [38,45].

The screw along with the entire length of barrel is typically divided into three sections. (A) *Feeding section*: The purpose of the feeding section is to transfer the materials from the hopper to the barrel. (B) *Compression or melting section*: Channel depth decreases in this section, so it creates pressure which removes entrapped air. The polymer typically begins to soften and melt in the compression zone. (C) *Metering zone*: When material comes to metering zone, the polymer blend already exists in the molten state. The function of the metering zone is to reduce the pulsating flow thus prevent the uneven material delivery to die and ultimately prevents the weight variation in final ODF formulations [38].

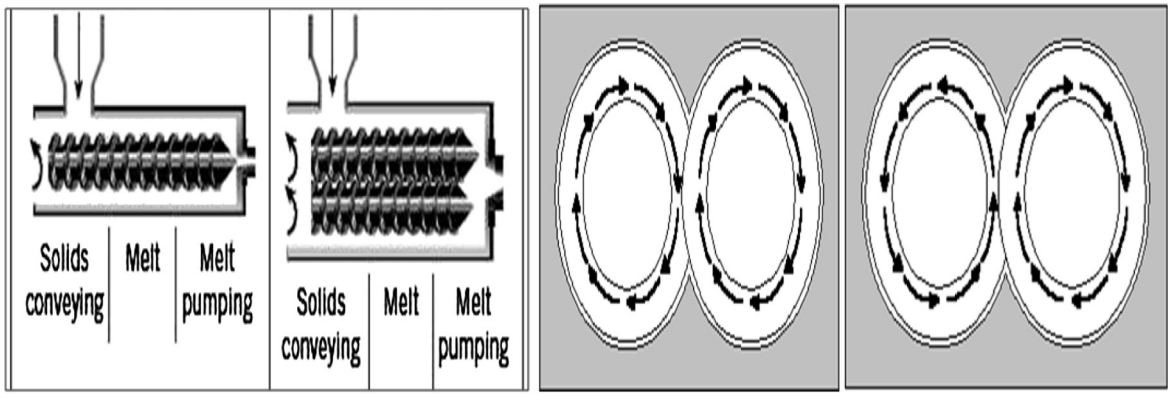

Fig. 1 – Schematic diagram of different variants of screw extruders.

2.2.3. *Side stuffing port provision*

In pharmaceutical industry, incorporation of heat sensitive actives and flavors are most difficult in ODF prepared by HME. This problem can be eliminated with provision of side stuffing port in barrel. The side stuffing port is just far enough from the die to allow homogeneous mixing of active with already molten polymer-plasticizer matrix but close enough to the die to reduce the exposure time to elevated temperature. Bruce et al. [46] reported incorporation of heat sensitive taste masked coated dextromethorphan hydrobromide granules in previously molten polymer plasticizer blend by side stuffing port which was just near to the die. So, API was not exposed to high temperature required for melting of polymers. In area nearby side stuffing port, mixing of API with already molten polymer-plasticizer blend is done at lower temperature compared to melting zone temperature. API and flavors are exposed to heat for few minutes because residence time inside the extruder is less.

2.2.4. *Gear pump*

If flow of molten mass from barrel to die is uneven and fluctuating, then it creates weight variation as well as uneven film formation which ultimately create content variability. To eliminate inevitable small fluctuations in extruder output and to assure consistent material flow into die, gear pump is installed in line between the end point of barrel and the die. The gear pump is positive displacement pump that precisely meters the melts to the die and that can build and maintain a constant output pressure. It can buffer inevitable small variations in material inflow and input pressure of the extruder [46].

2.2.5. *Die system*

Die is attached at the end of extruder. The shape of the die determines the physical form or final shape of the film [38].

2.2.6. *Downstream processing elements*

For ODF formulations, chill rolls and torque winders are used to rapidly cool and collect the extruded film ribbons. The melt comes out from die and flow through the wide thin gap, followed by calendaring, in which film is squeezed between two temperature-controlled rotating rolls. Sometimes downstream processing elements also play important role in final film appearance and physical properties of film.(A) *Effect of calendar temperature on film*: Bruce et al. [46] found that when the calendar temperature was too low (chilled to 15 °C); films were difficult to stretch resulting in thicker films. On other side, film stuck to the roll when temperature was set at 50 °C or more. The optimal temperature was found to be 30 °C–35 °C. Stretching of films from rolls became harder below optimum temperature range. (B) *Effect of distance between the calendaring rolls*: The gap between the calendaring rolls is the last influence in shaping the film before it cools into solid form. The gap setting was smaller than the desired film thickness, since the melt was elastic and swelled after emerging from the rolls [46–48].

3. Formulation considerations

Oral strip is ultrathin strip containing an active agent and mainly polymer-plasticizer with desired amount of color, flavor, sweetening agent and saliva stimulating agents. In HME, glass transition temperature of the polymer plays a decisive role in designing the process parameters. Therefore, rationalized selection of plasticizer is most important according to thermal behavior of polymer and most importantly thermal sensitivity of active [29,49]. Sometimes, sugar alcohols, stabilizers, antioxidants, slip agents or anti block agents and anti-sticking agents are added to make the process smooth [50,51].

3.1. *Film forming polymers*

The choice of an appropriate polymer is crucial for extrusion process. Polymers for hot-melt extrusion (HME) should have the thermoplastic behavior to enable melt extrusion to take place [52,53]. They should have a suitable glass transition temperature (Tg) in the range of 50–180 °C, low hygroscopicity, stability at extrusion temperature and no toxicity, since large amounts of polymer are used. In this section, polymers which are mainly used in oral strip technology are discussed with special emphasis on thermal stability and extrudability. In HME process, polymer acts satisfactorily with particular plasticizers. Hence, combined discussion of polymer and plasticizer is more appropriate than that of polymer alone.

3.1.1. *Polyethylene oxide*

Polyethylene oxide (PEO) is a white crystalline hydrophilic powder available in range of 100,000 to 7,000,000 Da molecular weight. PEO is widely accepted film former used in HME because of its broad processing window [54–56]. Bruce et al. [46] claimed the use of POLYOX WSR N-10 (Molecular weight about 100,000 Da, Dow Chemicals) and POLYOX WSR N-80 (Molecular weight about 200,000 Da, Dow Chemicals). Among all the grades, POLYOX WSR N-10 is most preferred for ODF formulations. Bruce et al. [57] reported extrusion process temperature for PEO is less than 100 °C, preferably between 50 and 60 °C. So for heat sensitive materials, PEO is advantageous. They evaluated combination of hydroxypropylcellulose (HPC) and PEO in different ratios with PEG 400 as plasticizer. Most preferred plasticizer for PEO is vitamin E derivatives. Repka et al. [38] prepared films containing HPC and PEO with and without vitamin E TPGS (D-alpha-tocopheryl polyethylene glycol 1000 succinate) as an additive. In addition, the presence of 3% vitamin E TPGS lowered the Tg over 11 °C when compared with the HPC/PEO 50:50 blend film without vitamin E TPGS. Vitamin E TPGS helped in processing of HPC-PEO blends by decreasing melt viscosity and reduction in frictional forces [38,58]. Fuisz [59] reported use of vitamin E and its derivative as stress crack eliminators during extrusion process. 5–10% of vitamin E and its derivatives are most preferred to eliminate the stress cracking of polymer film.

The thermal oxidation of PEO in the solid state has been characterized as an autocatalytic free radical process [60]. Crowley et al. [61] demonstrated different antioxidants like vitamin E and its derivatives, vitamin C (ascorbic acid) and butylated hydroxyanisole (BHA). The addition of 5% vitamin E succinate, 1% vitamin E and 30% vitamin E TPGS successfully retarded molecular weight loss of PEO. The color of the extrudates was unchanged. These compounds have previously been found to suppress free radical production in photo

irradiated pheolmelanin. In contrast, vitamin C and BHA did not stabilize PEO. Both vitamin E succinate and vitamin E TPGS decreased the torque during extrusion suggesting an improvement in polymer chain motion. However, BHA and vitamin E acetate were ineffective in stabilizing the molecular weight of PEO during extrusion. Bruce et al. [57] reported that disintegration time of PEO films were increased with increase in moisture content of polymer during long storage period. They hypothesized PEO crystallization in presence of water and this semi-crystalline film would be expected to have a longer disintegration time compared to a non-crystalline amorphous films.

3.1.2. *Maltodextrin*

Maltodextrin is a polysaccharide synthesized from starch by partial hydrolysis. Maltodextrin is widely accepted due to its low process temperature and high water solubility in ODF prepared by HME. Maltodextrins are classified by dextrose equivalent (DE) [62,63]. Dextrose equivalent is defined as measure of amount of reducing sugars present in relative to dextrose and calculated as percentage on dried basis. As the DE value increases, glucose chains length decreases and the sweetness of the maltodextrin increases with higher solubility and the lower heat resistance [64]. So, higher DE containing maltodextrins are generally preferred for ODF formulations [65–67]. Maltodextrin has miscibility problem with PEG. So, PEG is generally not used with maltodextrin [29]. Cilurzo et al. [68] evaluated film forming property of maltodextrins in solvent casting and hot melt extrusion. They used Glucidex IT12 (maltodextrin with DE value12) and the processing temperature throughout the extrusion process was 65–115 °C. Glycerol was incorporated as plasticizer to maltodextrin and piroxicam blend with microcrystalline cellulose as anti-sticking agent.

3.1.3. *Hydroxypropylcellulose*

Hydroxypropylcellulose is a non-ionic water soluble cellulose and combines dual solubility in aqueous and polar organic solvents, thermoplasticity and surface activity with the thickening and stabilizing properties of other water soluble cellulose polymers [69–71]. Among all grades, Klucel EF and Klucel LF are widely accepted for ODF due to its lower viscosity and lower processing temperature compared to other grades [21,22,72]. Mididoddi et al. [72] mentioned processing temperature for extrusion of HPC Klucel EF and LF was 150–160 °C. Mcginity et al. [73] claimed effervescent hot melt extruded polymeric films prepared with HPC extruded at temperature ranging from about 50 °C to about 180 °C. Fuisz [59] claimed smokeless tobacco film prepared with different concentration of Klucel EF, ELF and LF. 3–6% Propylene glycol of total dry weight of formulation was used for successful extrusion of HPC films.

3.1.4. *Hydroxypropyl methyl cellulose (HPMC)*

Hypromellose (HPMC) is hydrophillic polymer widely accepted in ODF prepared by solvent casting but not accepted in films prepared by HME [74–76]. The reason for seldom use of HPMC in HME is its glass transition temperature. Tg of hypromellose is 160–210 °C and shows degradation in excess of 250 °C in significant amount. HPMC has not so much pronounced difference between Tg and degradation temperature so it is itself a big challenge to extrude the HPMC in such a narrow processing window [58]. Incorporation of high amount of plasticizers in film formulations can broaden the processing window of polymer. Aldeman [77] suggested at least 30% w/w plasticizer should be used in successful extrusion of hypromellose. Still less work is done in the area of film forming ability of hypromellose.

3.1.5. *Pullulan*

Pullulan is most widely used polymer in films prepared by solvent casting method but least used and preferred polymer for HME. Chemically, pullulan is a polysaccharide consisting of maltotriose units and produced from starch by the fungus *Aureobasidium pullulans* [78]. Pullulan is white to off-white tasteless, odorless, non-toxic, non-carcinogenic powder which forms clear transparent film with considerable mechanical strength and it is biodegradable and impermeable to oxygen [79,80]. Due to these unique properties, pullulan is widely used in solvent casting and many commercial products [29,81,82]. Pullulan starts to decompose at 250 °C and chars at 280 °C. Due to high melting temperature and narrow processing temperature range, it is less preferred polymer. Fuisz [59] mentioned the use of pullulan with 20–30% of glycerin as plasticizer in hot melt extruded film.

3.1.6. *Starch and modified starch*

Starch is considered as good choice as a natural material widely used for extrusion [83,84]. Bruce et al. [46] reported the use of starch 1500, a partially pregelatinized starch, in extruded films. They reported poor film formation due to insufficient plasticization initially but optimum plasticization formed thin films with fast disintegration time. Still starch 1500 was considered as poor film former due to stickiness and brittleness in extruded films.

Modified starches are prepared by physical, enzymatic or chemical treatment of native starch [83]. Among these modified starches, hydroxypropyl starch (HP starch) is widely used in ODF preparation [85]. Bruce et al. [46] evaluated different modified starches for their film forming ability as well as rapid disintegration. They evaluated different grades of ready mix modified starches developed by Roquette pharma, e.g. Lycoat RS 720 (higher viscosity HP starch), Lycoat RS 780 (lower viscosity HP starch), Lycoat NG 73(pregelatinized HP starch), Lycatab PGS (completely pregelatinized starch), Lab 3455 (pregelatinized HP starch), Nutriose FM06 (maize dextrin soluble fibre) and powdered 400L (modified corn starch). Plasticizers like glycerin and sugar alcohols were added along with modified starch for smooth extrusion. Starch containing films have disintegration time higher than desired. So some amount of modified starches was replaced with either fillers like silicon dioxide, talc, microcrystalline cellulose and titanium dioxide or secondary film forming agent like maltodextrins and PEG 3350. In comparision to film containing alone starch, disintegration was faster and films with lower starch content disintegrate faster (average 17–26 s). The addition of PEG 3350 resulted in shorter disintegration time than addition of maltodextrins. But PEG containing films were brittle and tacky.

3.1.7. *Acrylic polymers*

Even though less work is done, acrylic polymers like Eudragit have potential for satisfactory film forming ability with HME.

Acrylic films prepared by solvent casting and evaporation of isopropyl alcohol showed decrease in plasticity and densification of film by evaporation of solvent during storage. This can be eliminated by solvent free HME process [86]. Aitken Nichol et al. [87] examined film forming ability of Eudragit E100 with triacetin, polyethylene glycol 6000 and triethyl citrate (TEC) as plasticizer. They reported the stability of Eudragit RS was adequate for extrusion at 130 °C. Wu et al. [88] reported smooth extrusion process of Eudragit RSPO at 90–115 °C with triethyl citrate as plasticizer.

3.2. Plasticizers

Polymers of high molecular weight exhibit a high melt viscosity and are difficult to extrude. Moreover, a high Tg requires a high processing temperature, which can degrade sensitive actives. As a general rule, an extrusion process should be run at a temperature 20–40 °C above the Tg [89]. Polymer properties can be adjusted by the use of plasticizers since these materials reduce the Tg and melt viscosity and also facilitate the extrusion process [90,91]. Polymers, their most preferred technical grades, merits and demerits of polymer and preferable amount of each plasticizer are summarized in Table 1.

3.3. Sugar alcohols

Sugar alcohols are soluble in water and saliva. Bruce et al. [57] reported that higher amount of sugar alcohols in film formulation can enhance the dissolution by creating porous matrix in strip. Sorbitol, xylitol, mannitol, lactitol, maltitol and erythritol have been reported as sugar alcohols in ODF. Among these all, sorbitol (melting point 95 °C) and mannitol (melting point 167 °C) are most preferred.

3.4. Antisticking agents

During the extrusion process, high shear force is generated due to frictional forces which ultimately generate excessive heat generation and thermal fluctuations during process. Addition of antisticking agents like microcrystalline cellulose is most preferred method to eliminate this problem. It is hypothesized that retained moisture by MCC exerts lubricating activity resulting in reduced frictional forces. Cilurzo et al. [68] reported higher disintegration time of piroxicam-maltodextrin ODF containing MCC (45 s) as compared to ODF without MCC. Swelling tendency of MCC also retarded dissolution of piroxicam from ODF.

3.5. Sweetening agents

Natural sweeteners like glucose and fructose are less preferred in HME due to their charring tendency at high temperature. Sucralose, acesulfame potassium, alitame and neotame are preferred due to its low concentration in total formulation [92].

3.6. Saliva stimulating agents

Saliva stimulating agents are used to increase the rate of production of saliva that would aid the faster disintegration of ODF [29]. Citric acid, malic acid, lactic acid, ascorbic acid and tartaric acid are few examples of salivary stimulants. Citric acid has melting point around 100 °C and softens at 75 °C [93].

3.7. Anti-block agents and flow promoters

The anti-block compounds are used to prevent film roll blocking during extrusion cycle. As per the flow characteristic of polymer plasticizer blend, required amount of flow promoters like silicate derivatives can be added to the formulation [59].

3.8. Flavors and taste masking agents

Incorporation of heat sensitive flavors is most difficult with ODF prepared by HME. This problem can be eliminated with provision of side stuffing port in barrel as discussed in section 2.2.3 [46]. Solid dispersion of bitter tasting drugs is reported with hot melt extrusion. Eudragit EPO and ethyl cellulose are some of the widely used polymers that can mask the bitter tasting API by solid dispersion prepared by HME [94,95].

4. Problems found during development and scale up of ODF made by HME

4.1. Die swell phenomenon

The cross section of the film increases upon leaving the die depending upon the viscoelastic property of polymers. So, final dimension of the film changes due to this 'Die swell phenomenon'. Mechanism behind the phenomenon is that polymer is exposed to high shear force and high energy kneading during extrusion. So, polymer comes in state of stress and after completion of extrusion process, polymer tries to come in to relaxation state by increasing their radius of gyration [38]. So, the dimension of final formulation is slightly changed. This problem can be eliminated by slow speed screw operation with slow kneading as well gentle mixing for long time rather than high shear kneading for short duration.

4.2. Fish eye formation

Sometimes due to flavors or residual moisture in ingredients e.g. natural or phytochemicals products, the blend has inherent tendency to agglomerate. Agglomerate type of uneven, irregular and non-uniform formation in the blend is called 'Fish eye'. Once 'fish eye' or agglomerations are formed, they are extremely difficult to eliminate from the blend. It will create uneven pulsatile flow as well as uneven temperature distribution in barrel. To eliminate 'Fish eye' formation in blend, high shear mixing must be employed from beginning. Fuisz [59] reported incorporation of silica derivative e.g. calcium silicate to avoid fish eyes in tobacco containing blend.

4.3. Incorporation of liquids with powder blend

In some cases, liquid ingredients (e.g. plasticizers like PEG, PG and glycerin) are required for smooth extrusion process. First method of incorporating liquid to polymer blend is

Table 1 – Polymers, plasticizers and their extrusion characteristics.

Polymers	Characteristic property	Technical grades used in melt extruded ODF	Processing temperature range	Most preferred plasticizer	Advantages	Disadvantages and remedies
Polyethylene Oxide	White crystalline hydrophilic powder	Polyox WSR-N10 and Polyox WSR-N80	Crystalline melting point is approx. 70 °C and preferable processing range is 50–60 °C	Low molecular weight PEG (7–15% W/W of dry polymer weight) and Vitamin E TPGS	Due to its low processing temperature range, it is advantageous for heat sensitive actives.	Thermal oxidation is generally shown in PEO film. So, antioxidants are generally added in formulation
Maltodextrin	White powder or granular polysaccharide synthesized from partial hydrolysis of starch.	Technical grades with dextrose equivalent (DE) no. 3 to 20, preferably DE 6 and DE 12	Preferable processing range is 65–115 °C	Glycerol (16–20% W/W) and propylene glycol most widely preferred. PEG is not preferred due to miscibility problem with maltodextrin	Low processing temperature range is advantageous for thermolabile materials. High water solubility enhances quick disintegration.	Antimicrobial preservatives are required due to its natural carbohydrate origin. Under certain condition of pH and temperature, it may undergo Maillard reaction with amino acids. Incompatible with strong oxidizing agents
Hydroxy propyl cellulose (HPC)	White to off white colored, non-ionic water soluble cellulose derivatives	Klucel EF and LF due to its low viscosity and low processing temperature compared to other grades	Softens at 130 °C and chars at 260–275 °C. Processing temperature range is 150 –160 °C.Taioloring with processing window is possible with appropriate plasticizers.	Propylene glycol (3–6%W/W or more as per product requirement)	Good thermoplastic behaviour, self plasticizing behavior (less amount of plasticizer) is required. Good tensile strength even at low viscosity grade	Processing temperature is comparatively high so selection of plasticizer is crucial.
Hypromellose	Hydrophilic water soluble polymer	HPMC E3, E6 and E15 are widely used polymers	No significant difference between Tg and degradation temperature. Very critical to extrude in such narrow processing temperature range.	Up to 30% or more plasticizer is required to broaden the processing window. PEG grades and PG are widely accepted with Hypromellose.	–	Very high concentration of plasticizer is required to extrude film

Pullulan	White to off white tasteless polysaccharide produced from starch	–	Starts to decompose at 250 °C and chars at 280 °C. Very high processing temperature (>100 °C) required.	Glycerin (20–30% W/W)	–	Processing temperature is comparatively high so selection of plasticizer is crucial.
Modified starch	Physical, enzymatic and chemically modified starch	Hydroxy propyl starch	80–95 °C	Glycerin	–	Comparatively low tensile strength of film so, selection of plasticizer is crucial.
Acrylic polymer	Poly(meth)acrylate derivatives	Eudragit RSPO and E100	90–115 °C for Eudragit RSPO and 80–110 °C for Eudragit E100	PEG 6000 and Triethyl citrate	–	–

granulation. Cilurzo et al. [68] reported granulation of piroxicam, maltodextrins and MCC blend with glycerol. Bruce et al. [46] reported granulation of PEO with PEG 400 to improve the flow. Granulation method can provide uniform mixing and improved flow property but it will create multistep processing which is considered uneconomical from industrial aspect. Second method is side stuffing. After molten mass formation inside the barrel, liquid is incorporated via side stuffing port. Bruce et al. [46] reported direct incorporation of PEG 400 into barrel after melting of solid components in compression zone.

4.4. *Weight variation within film sheets*

Sometimes uneven films are formed due to improper flow of powder blend through hopper. So to improve the flow property of power blend, either granulation method as discussed in section 4.3 or force feeder can be employed. In some cases, glidants are added in dry mix blend. Fuisz [59] claimed the addition of 3–5% silicates to promote the flow of tobacco blend containing high moisture content phytochemicals. If weight variation is due to the uneven pulsatile flow of molten mass, gear pump provision should be provided near to end of barrel.

4.5. *Chemical stability of active during hot melt extrusion*

During hot melt extrusion process, many chemical reactions like hydrolysis and solvolysis due to residual moisture and solvent as well as free radical generation are initiated at elevated temperature. To solve the issue of residual moisture and solvent, preheated excipients are sometimes used in process. To eliminate generation of peroxides and free radicals, antioxidants like vitamin E TPGS, butylated hydroxy toluene and butylated hydroxyanisole are generally added to blend [38,42].

4.6. *Recrystallization and nucleation of drug molecules*

At elevated temperature, pressure and intense mixing, solubility of active in polymer blend is increased but recrystallization of active molecule from the molten blend occurs after temperature drop. This problem can be prevented by preparing highly viscous molten polymer plasticizer medium [38].

5. Development strategies as per quality by design

Quality by Design (QbD) is a concept outlined by Joseph M. Juran who believed that quality could be planned and that most quality crises and problems related to the way in which quality was planned [96,97]. Here hypothetical summary of ondansetron fast dissolving film 25 mg is taken as an example for pharmaceutical development report illustrating QbD compliant data to FDA. In successive part, introductory discussion covering QTPP, CQA, CMA and CPP are identified to understand product and process thoroughly.

(A) *Quality target product profile* (QTPP): Definition as per ICH is "QTPP is a prospective summary of the quality

Table 2 – Quality target product profile for ondansetron fast dissolving film.

QTPP elements	Target	Justification
Dosage form	Film	Pharmaceutical equivalence requirement: same dosage form as reference listed drug (RLD)
Dosage form design	Fast dissolving single layer oral film	Pharmaceutical equivalence: same as reference listed drug (RLD)
Dosage strength	4 mg, 8 mg	Same strength as RLD
Route of administration	Oral	Pharmaceutical equivalence requirement: same route
Pharmacokinetics	Immediate release	Bioequivalence requirement. Needed to ensure quick onset and efficacy
Stability	At least 24-month shelf-life at room temperature	Equivalent to or better than RLD shelf-life
Container closure system	Triple laminated aluminum child resistant pouch	Needed to achieve the target shelf-life
Film Shape	Rectangular film	Pharmaceutical equivalence requirement: same as RLD
Administration/Concurrence with labeling	Prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy: The adult oral dosage is 24 mg given successively as three 8 mg films 30 min before the start of chemotherapy	Pharmaceutical equivalence requirement

Table 3 – Critical quality attributes for generic ondansetron fast dissolving film.

Quality attributes of the drug product	Target	Is this a CQA?	Justification
Appearance	Color and shape acceptable to the patient. No visual film defects	No	Color, shape and appearance are not directly linked to safety and efficacy. So, they are not critical. The target is set to ensure patient acceptability.
Odor	No unpleasant odor	No	Odor is not directly linked to safety and efficacy, but odor can affect patient acceptability. For this product, neither the drug substance nor the excipients have an unpleasant odor.
Size	Similar to RLD	No	For ease of administration to oral cavity
Flavor and taste	No unpleasant bitter taste	Yes	Taste is not directly linked to safety and efficacy, but bitter taste of API can affect patient acceptability.
Disintegration time	Similar to RLD	Yes	Quick onset and efficacy is directly linked to disintegration time of film in oral cavity.
Identification	IR/UV/Chromatography	No	Though identification is critical for safety and efficacy, this CQA can be effectively controlled by the quality management
Assay	100% w/w of label claim	Yes	Assay variability will affect safety and efficacy. Process variables may affect the assay of the drug product. Thus, assay will be evaluated throughout product and process development.
Uniformity of weight and content	Complies to pharmacopoeial specification	Yes	Variability in content uniformity will affect safety and efficacy.
Dissolution	Complies to pharmacopoeial specification	Yes	Failure to meet the dissolution specification can impact bioavailability. Both formulation and process variables affect the dissolution profile. This CQA will be investigated throughout formulation and process development.
Degradation products	Complies to compendial specification or ICH requirements	Yes	Degradation products can impact safety and must be controlled based on compendial/ICH requirements or RLD characterization to limit patient exposure. Therefore, degradation products will be assessed during product and process development.

characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product." It relates to quality, safety and efficacy, considering e.g., the route of administration, dosage forms, bioavailability, strength and stability [98,99]. Form for identifying QTPP is given in Table 2.

(B) *Critical Quality Attributes* (CQA): Definition as per ICH is "CQA is a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality." [99–101] CQA for ODF prepared by HME is outlined in Table 3.

(C) *Critical Process Parameter* (CPP): Parameters of the process that must be maintained in a narrow range to ensure acceptable product quality is called critical process parameters [102]. CPP for hot melt extruded film is given as flow diagram in Fig. 2.

(D) *Critical material attributes* (CMA): A physical, chemical, biological and microbiological property of raw material,

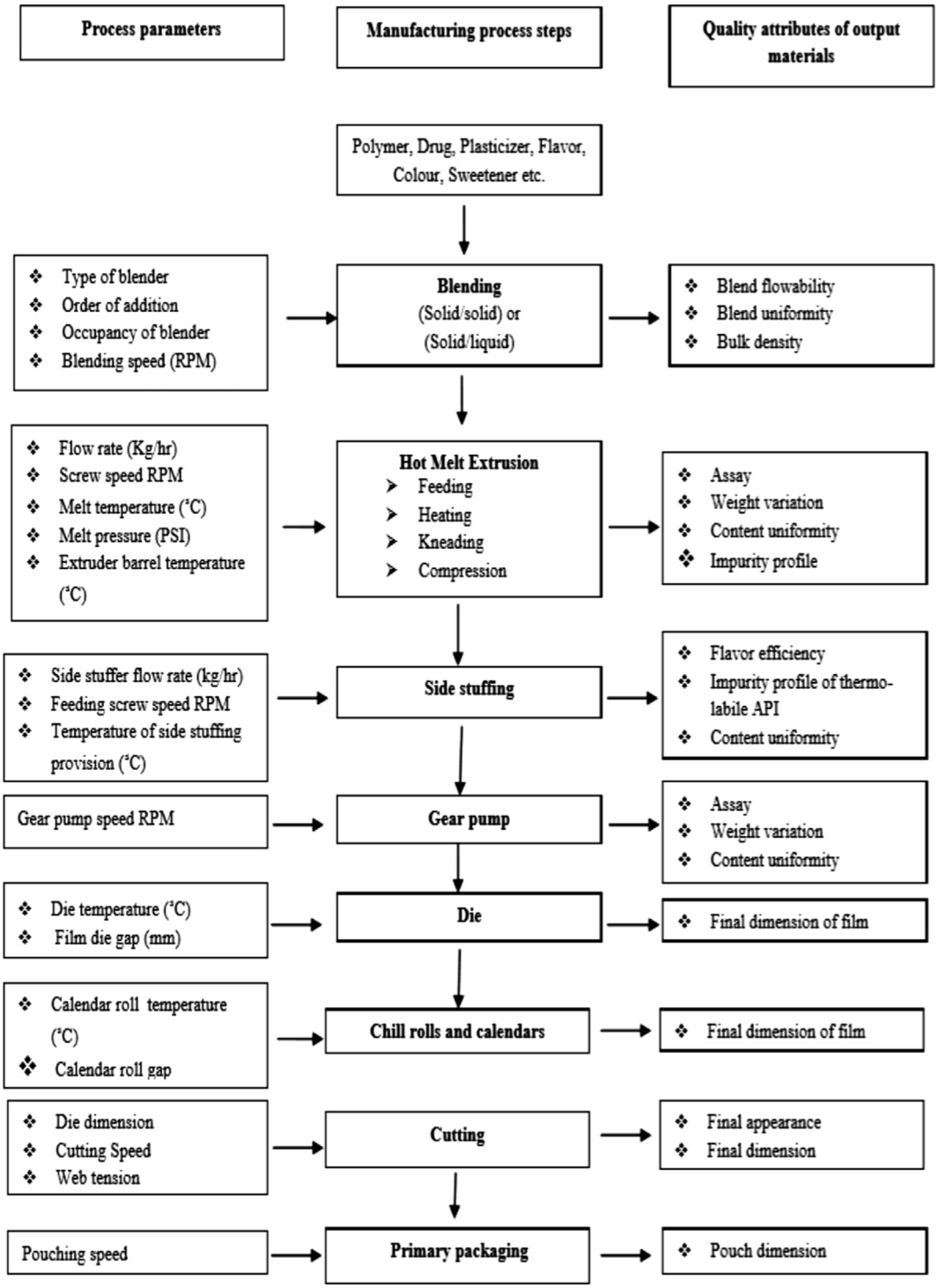

Fig. 2 – Process mapping for identification of critical process parameters.

starting material, reagents, solvents, processing aids, active, packaging and labeling materials that can affect the product throughout its life cycle is considered critical material attributes [99–101]. CMA for active used in melt extruded film is enlisted in Table 4.

6. Scale up consideration and dimensional analysis

A chemical engineering is generally concerned with the industrial implementation of hot melt extrusion processes [103,104]. HME processes are scale dependent means they behave differently on a small scale and on a large scale. Understandably, formulation scientists have always wanted to find ways of simulating these processes in models to gain insights. So small scale and production scale operation can be simulated [105].

6.1. *Dimensional characterization of screw*

The design and dimension of the screw within heated barrel has significant impact on process. The dimension of the screw is given in terms of L/D ratio means length of screw divided by diameter. Typical extrusion process lengths are in the 20 to 40: 1 L/D ratio [44]. As per the batch size, 18–27 mm extruders in pilot scale and 60 mm extruder in production scale is preferred. Here increase in screw size is approximately 2 folds but extruder output is increased 10 fold at production level by doubling the screw size of pilot scale machine [38].

6.2. *Scale-up model calculation and machine selection*

6.2.1. *Throughput rate calculation*

From entry of blend in hopper to final cutting of extruded ribbon in strip form, Scale-up is useful for estimating rates for production in twin-screw extruders [45]. For processes that scale-up geometrically, the equation is as follows

$$\text{Scale up—Power based}: \; Q_{target} = Q_{reference} \times [(OD_{target})/(OD_{reference})] \quad (1)$$

Where, Q_{target} = Throughput rate in target system (Production scale) (kg/hr), $Q_{reference}$ = Throughput rate in target system (small scale) (kg/hr) and OD = Outer diameter of screw of production scale and small scale extruder

For processes that scale-up volumetrically, the equation is as follows

$$Q_{target} = Q_{reference} \times (SV_{target}/SV_{reference}) \quad (2)$$

Where, Q_{target} = Throughput rate in target system (Production scale) (kg/hr), $Q_{reference}$ = Throughput rate in target system (small scale) (kg/hr) and SV = Specific volume of production scale and small scale extruder in cc/diameter

6.2.2. *Shear rate*

Shear rate is defined as the velocity gradient between two surfaces moving at different speeds [45].

$$\text{Peak shear rate} = (\pi \times D \times n)/(h \times 60) \quad (3)$$

Table 4 – Identification of Critical material attributes of API, quality risk assessment – risk ranking and risk filtering.

Quality Attributes	Risk assessment			Category* (Critical/Noncritical)	Remarks
	Severity	Probability	Risk Score		
Polymorphism	3	3	9	H	Can impact CQAs. Effect on efficacy and stability.
Assay	1	1	1	L	Can impact CQAs. Will be controlled through specification.
Impurity profile	3	3	9	H	Can impact CQAs. Stability data and forced degradation data suggest that at higher temperature, significant increase in impurity found.
Melting point	2	2	4	M	Can impact CQAs. Will influence process parameters of HME.
Moisture level	1	1	1	L	No impact on CQAs.

Risk assessment and risk filtering

Score	Severity	Probability	Risk matrix Probability Severity	1	2	3
1	Minor	Low	1	L	L	M
2	Major	Medium	2	L	M	H
3	Critical	High	3	M	H	H

* Score 1–2: Noncritical, Score 3–4: Medium critical, Score 6 or above: Critical.

Where, D = screw diameter, n = screw speed in rpm and h = over flight clearance.

6.2.3. *Shear stress*

The shear stress is the magnitude of the applied stress that the material experiences as a function of the shear rate and viscosity [45].

$$\text{Shear stress} = \text{Viscosity} \times \text{Shear rate} \quad (4)$$

6.2.4. *Barrel temperature, melt viscosity and mixing efficiency*

Barrel temperature is increased or decreased to manage the viscosity of the melt, which impacts the mixing quality. Cooling is often used to raise the viscosity [46].

6.2.5. *Specific energy*

Specific energy (SE) is defined as the amount of power that is consumed by the motor into each kilogram of material being extruded [45].

6.2.6. *Residence time (RT)*

The RT provides tentative idea about how long materials are exposed to heat and shear in the process section. Generally extruder residence times are between 5 s and 10 min [45,47].

6.2.7. *Temperature shoot-up during pressure generation*

Due to very restricted area at die, very high pressure is generated which ultimately create sudden temperature rise [45]. The temperature rise is denoted by following equation:

$$\Delta T\,(^{\circ}\text{C}) = \Delta P\,(\text{bar})/2 \quad (5)$$

Here, ΔT = change in temperature in °C and ΔP = change in pressure (1 bar = 14.503 psi).

7. Conclusion

Though solvent casting is widely accepted method by formulation scientist to cast Orodispersible film, hot melt extrusion has immense potential for the same. In this article, common problems found during the scale up and their remedies are thoroughly discussed which will be helpful for voyage of film formulation from lab scale instruments to heavy duty production scale continuous process machines. Till date less work has been done in HME compared to solvent casting but rationalized selection of process and excipients will makes HME as method of choice for ODF formulation in future.

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