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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.