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Taste masking of bitter pharmaceuticals by spray drying technique

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ABSTRACT

Taste masking has gained immense significance in the formulation of bitter taste medicaments and is being tackled early in the product development to offer multiple benefits to both the patients as well as the pharmaceutical manufacturers. Taste masking is a viable and practical strategy to improve the patient compliance, especially for bitter drugs, whereby, a number of methodologies may be adopted to deliver a taste masked palatable formulation. Various techniques based on different principles have been investigated and described in academic and patent literature for masking of bitter or undesirable taste of drugs like addition of flavors, sweetener and amino acids, microencapsulation, complexation with cyclodextrins, complexation with ion exchange resin, salt preparation, group alteration and prodrug approach. In the present review, the spray drying has been presented as a viable technique for taste masking of bitter pharmaceuticals. The manuscript comprehensively describes the spray drying methodology, its instrumentation, characterization and application in pharmaceutical taste masking.

Key words: taste masking; patient compliance; spray drying; bitter drug; inlet temperature

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INTRODUCTION

Taste is one of the most important parameters governing patient compliance. A wide variety of active pharmaceutical agents exhibit the bitter taste either during or immediately after oral administration resulting in poor compliance. Although the poor drug compliance due to bitter tasting oral drugs is true for all patient populations, but is significant for pediatric and geriatric medications [1]. The poor palatability and bitter taste were found to be one of the main reasons for non-compliance resulting in a lot of revenue loss to pharmaceutical companies [2-3]. This further result in discontinuities in therapy as the bitter taste causes resistance in swallowing oral drugs thereby losing the beneficial effects of the drug [4]. Low loyalty to OTC brands, frequent medication switch and overall loss in revenues are the other issues arising out of low compliance.

Taste masking is a viable and practical strategy to improve the patient compliance, especially for bitter drugs, whereby, a number of methodologies may be adopted to deliver a taste masked palatable formulation. The development of taste masked pharmaceutical product also makes a lot of business sense as any pharmaceutical formulation with a pleasing taste would definitely be preferred over a competitor's product. This not only enhances the compliance and therapeutic value for the patient but also generate more business and profits for the company [5]. The desire of improved palatability in these products has prompted the development of numerous bitter taste masked formulations with improved performance and acceptability [6]. Several techniques have been reported for masking of bitter or undesirable taste of drugs like addition of flavors, sweetener and amino acids, microencapsulation, complexation with cyclodextrin, complexation with ion exchange resin, salt preparation, group alteration and prodrug approach [7-10]. Spray drying has also emerged as one of the simple and viable approach for taste masking.

In the present article, the technique of spray drying and its application in pharmaceutical taste masking has been reviewed. The present work is also focused on the basics of spray drying technique and various factors influencing the development of taste masked pharmaceutical formulation by spray drying.

SPRAY DRYING TECHNIQUE: INSTRUMENTATION AND BASIC METHODOLOGY

Spray drying can be defined as conversion of a feed from a fluid state into dried particulate form by subjecting the feed to a hot drying medium. Various liquids such as solution, emulsions, dispersions, slurries or even melts can be directly transformed into solid particles with desired properties such as size, distribution, shape, porosity and density by spray drying method [11-12]. The various advantages of spray drying are enlisted in Table 1.. The spray drying process generally consists of a sequence of four steps [13-14]:

- Feed preparation
- Atomization/droplet formation
- Drying, particle shape formation and drying
- Separation of dried product

The first component of spray drying process is the feed in the form of an emulsion, suspension or solution. The spray drying is a four step process involving feed preparation, atomization of liquid stream, subjecting the droplets to the interaction with a drying gas and finally separating the dried particles by an appropriate device to obtain the spray dried product. The solid product is formed by removal of solvent contained within the dispersion during the drying phase. During the last phase, the dried particles are separated and collected by a receptacle tank. All the phases and the processing conditions of each phase affect spray drying process efficacy and the characteristics of the final dried product [15]. The basic components of a spray dryer are illustrated in Figure 1 and the details of aforementioned basic steps in spray drying are as follows:

Feed preparation

The first component of spray drying process is the feed which can be an emulsion, suspension or solution made up of a solvent and substances requiring spray drying. The feed is normally prepared by dissolving the bitter drug and the taste masking polymer in a co-solvent [13].

Atomization

The term atomization refers to the reduction of particle size of feed in fluid state. Several types of devices can be used for atomization. The basic devices include rotary atomizers; hydraulic (pressure) nozzles; pneumatic nozzles and ultrasonic nozzles. Various types of pumps such as peristaltic pumps can be used to transport the feed to the atomization device. The physical properties of the feed such as viscosity must be controlled to allow uniform, repeatable feeding and avoid clogging problems. The selection criteria of atomizer are mainly based upon the substance to the spray dried and its desired properties after drying [13].

Drying, particle shape formation and drying

After atomization, the next step is exposure of liquid feed to the drying gas. The drying gas is air which is taken from atmosphere, filtered and pre-heated before it reaches the drying chamber. The inlet temperature of the drying air is critical for the removal of solvent from the liquid feed. The inlet temperature is adjusted to optimum level to obtain the desired product without the risk of burning the product. The humidity along with temperature of air is also controlled to enhance the performance and efficacy of drying process [14]. The manner in which the sprayed liquid droplets contact the drying gas is significant in spray drying process. Co-current, counter current and combination mode are various flow configurations in spray dryers. The co-current mode is the one in which the material is sprayed in the same downwards direction as the flow of the hot gas. In this mode, the droplets contacts with the hot gas at the top, and leaves the spray chamber at the bottom where the gas temperature is lowest. In counter current mode, the spraying of the material is in the opposite direction to the hot gas. In this mode, the hot gas enters at the bottom and flows in upwards direction in the spray chamber. The co-current dryer is the most practical and useful mode of drying. Co-current chambers are used on the industrial scale for drying at considerably high temperatures without over-heating the product [13].

Separation of dried product

After the drying process, the product particles settle down at the bottom of the drying chamber. The settled dried product is then collected by appropriate devices. The fine particles that may leave the chamber together with the

outgoing air are retained in cyclone or filter bags. The product collected at the bottom requires internal scraper device for collection. Other devices such as vibratory, mechanical brushes and stream of air can also be used as scrapers for product collection. The use of scraper devices is necessary when the configuration of the drying chamber is such that it does not allow the free flow of the product [14].

The collected product is in the form of microspheres in which the bitter drug is encapsulated/entrapped in a polymeric matrix The spray dried microspheres does not allow the drug to be released at salivary pH thus masking the bitterness in oral cavity. However, active drug is then rapidly released afterwards in gastric fluids. Thus, the taste is masked without interfering with the release of drug in gastric environment which make it very suitable technique for taste masking of immediate release dosage forms meant for oral administration.

FACTORS AFFECTING SPRAY DRYING TECHNIQUE

The efficiency of spray drying process is affected by various factors such as inlet temperature, outlet temperature, flow rate of drying gas, feed rate and feed concentration [11, 16]. These factors are discussed in detail as follows:

Inlet Temperature

The inlet temperature of the drying air is the temperature when the feed contacts with drying medium. The ability of feed to dry is dependent upon the thermal charge of this air and the inlet temperature also has the influence on the amount of solvent that may be removed per unit time. The inlet temperature is measured in front of the drying air entry into the drying chamber. This parameter affects the product properties in a feed-dependent manner [16].

Outlet Temperature

The outlet temperature is dependent upon the inlet temperature, drying gas flow rate and solid concentration in the liquid stream. Practically, it is the highest temperature to which the product may be heated. The outlet temperature is measured before the entry of the air carrying the product into the separation device. The outlet temperature governs the sizing of powder recovery equipment, and the higher the outlet air temperature, the larger will be the size of powder recovery equipment and conveying ducts and plenums. The outlet air temperature controls the final moisture content of the powder [14].

Flow rate of drying gas

The amount (volume) of drying air supplied to the system per unit time constitutes the drying gas flow rate. The drying level of the product and its separation in the cyclone is dependent on the flow rate of drying gas. The lesser drying air feed rate slows down the movement of the product particles through the system which require longer action of drying air. The drying air flow rate is generally adjusted to the maximal value available in order to maximize the cyclone operation efficiency [14].

Feed rate

Temperature difference between the inlet and the outlet is affected by the feed rate. The pump rate corresponds directly to the inlet mass. The higher the inlet mass, the more will be energy required to evaporate the liquid droplets to form solid particles [14, 16].

Feed concentration

The increase in solid feed concentration means less liquid is available to vaporize, and leads to increased outlet temperature resulting in spray dried product with large particle size. Care must be taken with high solid loadings (above 30%) to maintain proper atomization to ensure accurate droplet formation [16].

APPLICATION OF SPRAY DRYING IN TASTE MASKING OF PHARMACEUTICALS

Spray drying has lot of applications in pharmaceutical formulation development [17-18]. The spray drying has found application in taste masking of bitter drugs such as acetaminophen, ondansetron hydrochloride, donepezil hydrochloride, sildenafil citrate, famotidine and sumatriptan succinate. The details of taste masking of these drugs by spray drying method are explained as follows:

Reuter and Blank patented therapeutic taste-neutral powder form of obtained by spray-drying a suspension of colloidal silica in a lower alkanol solution of acetaminophen and ethyl cellulose. The spray dried drug product with neutral taste was further formulated into chewable tablets and fast dissolving dosage forms [19]. Tai, prepared spray dried taste masking composition containing spheroidal microcapsules (150 microns in diameter). The taste masking

composition comprised of a microcapsule core of sucralfate, a polymer soluble in the gastric fluids, bulking agent and a lubricating agent present from 0.1% to ~ 7%. Excellent taste masking ability was exhibited by the the microcapsules [20]. Mark *et al.,* developed paracetamol taste masked composition by spray drying technique. Ethyl cellulose of less than 23% by weight of the total weight of the composition was selected as coating material. Spray drying of the paracetamol and ethyl cellulose in the solvent was achieved by spraying a stream of air into an atomised suspension so that solvent is caused to evaporate leaving the paracetamol coated with the ethyl cellulose. The spray dried taste masked paracetamol was formulated as sachets, chewing gums, chewable tablets, gums, lozenges, liquids, suspensions and filled capsules [21]. Zgoulli *et al.,* investigated the feasiblity of a one-step spray-drying process to microencapsulate bitter tasting drugs, erythromycin and clarithromycin, antibiotics known to have an extremely bitter taste. Mixtures of clarithromycin (5% by weight) or erythromycin (30% by weight) with a biodegradable polymer were prepared and spray-dried under specific conditions of temperature and turbine speed. This process resulted in the microencapsulation of 80% of each drug as determined by high pressure liquid chromatography. Particle size was obtained in the range of 1 to 80 µ as determined by electron microscopy. The results showed the feasibility of microencapsulation of macrolides using a spray-drying technique [22]. Cumming developed taste-masked immediate release micromatrix powders formed by spray drying the drug and cationic copolymer synthesized from dimethylaminoethyl methacrylate and neutral methacrylic acid esters. The taste-masked powder was further incorporated into conventional oral dosage forms such as sprinkles, suspension, fast melt tablets, chewable tablets or effervescent tablets [23]. Bora *et al.,* employed spray drying technique to develope the taste-masked microspheres of intensely bitter drug ondansetron hydrochloride (OSH) using three different polymers viz. Chitosan, Methocel E15 LV, and Eudragit E100. The microspheres were also investigated for the effect of different polymers and drug-polymer ratios on the taste masking and drug release properties. The Eudragit microspheres in a 1:2 drug-polymer showed excellent taste masking, whereas, chitosan microspheres depicted the taste masking at 1:1 drug-polymer ratio. No taste masking was achieved in methocel microspheres at all the drug-polymer ratios. About 96.85% of drug release was obtained for eudragit microspheres and 40.07% for Chitosan microspheres in 15 min [24]. Xu *et al.,* developed taste masked microspheres of the model compound (famotidine) with taste masking material using spray drying and further incorporated them into orally disintegrating tablets. Central composite design was utilized to optimize the spray process was for two variables to obtain microspheres with desirable characteristics. Then optimized microspheres were formulated into orally disintegrating tablets. Solid concentration of 34mg/ml and feed rate of 7ml/min were found to be the optimal spray-drying process parameters. the spray-dried microspheres obtained showed the drug encapsulation efficiency in the ranges of 37.59 to 61.56%, with a mean diameter of less than 10 micron size and low moisture content (less than 4%). Bitterness evaluation study by a panel of six human volunteers found the taste of microspheres incorporated orally disintegrating tablets to be significantly improved. Moreover, the bioavailability of famotidine from the microspheres was not found to be decreased in an *in vivo* study in rats [25].

Yan *et al.,* developed taste masked orally disintegrating tablet (ODT) of donepezil hydrochloride (DH) for enhanced patient compliance. Microspheres with different ratios of drug and Eudragit® EPO were preparing using spray drying method to achieve taste masking. It was revealed that the microspheres with a drug–polymer ratio of 1:2 inhibited the release of DH in simulated salivary fluid thereby masking its bitter taste. The orally disintegrating tablets were prepared by formulating microspheres with 10% Polyplasdone NF and Low substituted Hydroxypropyl Cellulose (L-HPC) as superdisintegrating agents. The formulated tablets showed better disintegration than marketed formulation and significant improvement in taste was found in a bitterness evaluation test by human panel study [26]. Sheshala *et al.,* developed microspheres using Eudragit EPO polymer to mask the intensely bitter taste of sumatriptan succinate and incorporated them into formulated orally disintegrating tablets (ODTs). The technique of spray drying was used to prepare the taste masked microspheres. The resulting microspheres were formulated into ODT by mixing with different superdisintegrants in varying concentrations. The tablets were prepared by direct compression method followed by sublimation technique. The *in vitro* disintegration of all the tablet formulations was found to be within 37—410 s. The optimized formulation containing 5% Kollidon CL-SF was found to have a pleasant taste and mouth feel in human panel taste studies and disintegrated in the oral cavity within 41 s [27]. Hoang *et al.,* utilized sodium caseinate and lecithin to produce and characterize taste-masked powders of bitter drug acetaminophen by spray drying technique. Taste assessment was done by an *in vitro* method with a syringe pump using small volumes of aqueous medium and low flow rates, to mimic the behaviour in the mouth and compared to the electronic tongue analysis. Higher content in lecithin results in higher taste-masking efficiency. The combination of sodium caseinate and lecithin was found to be promising in masking the bitterness of acetaminophen [28]. In another study, Hoang *et al.,* also investigated calcium caseinate in association with lecithin in order to encapsulate the acetaminophen through spray-drying to mask the bitter taste for pediatric medicines. The spray flow, amount of

calcium caseinate and lecithin amount had significant effects on the release of drug during the first 2 min as revealed by a 2(4)-full factorial design. The increase in the spray flow and/or the calcium caseinate amount led to an increase in the amount of drug released and vice-versa. Calcium caseinate-based formulations resulted in decreased initial release of drug which effectively resulted in taste masking of drug [29]. Yi *et al.,* masked the bitter taste of sildenafil citrate (SC), a well-known phosphodiesterase-5 inhibitor used for erectile dysfunction (ED) and pulmonary artery hypertension (PAH) by developing particulate taste-masking system. The taste masked system comprised of microcapsules prepared by microencapsulating a gastro-soluble polymer, Eudragit(®) E100 (E100), at four different weight ratios (2:1, 1:1, 1:2, and 1:3) using the spray drying technique. Electronic tongue (e-tongue) system and the in vivo human panel sensory test were employed to evaluate the taste masking efficiency of the developed microcapsules. Further, the effect of polymer ratio on the taste masking of prepared microcapsules was also investigated. E100 was not found to interfere with the drug release in stomach in a dissolution studies at pH 1.2 buffer. Taste evaluation studies revealed a good correlation (R(2)=0.9867) between the weight ratio of polymer and the taste masking efficiency expressed in the distances on the PCA map of the e-tongue data [30].

Spray drying method has shown tremendous application in taste masking of several bitter drugs. Some extremely bitter drugs such as ondansetron hydrochloride, donepezil hydrochloride, sildenafil citrate, famotidine and sumatriptan succinate has been effectively taste masked by this technique and further incorporated into orally disintegrating tablets or suitable dosage form. **CHARACTERIZATION OF SPRAY DRIED PRODUCT**

Following is a brief account of various techniques and methods employed for characterization of the spray dried product:

Entrapment efficiency, drug loading and percentage yield

The entrapment efficiency and drug loading in microspheres is estimated by first assaying the product for drug content by suitable analytical techniques such as HPLC, UV Spectroscopy and HPTLC. The entrapment efficiency, drug loading and % yield are then calculated according to the following equation [31]

$$\text{Loading capacity (\%)} = \frac{\text{Mass of drug in microspheres}}{\textit{Mass of microspheres recovered}} \times 100 \quad \text{---- Eqn. 1}$$

$$\text{Encapsulation Efficiency (\%)} = \frac{\text{Mass of drug in microspheres}}{\text{Mass of drug in formulation}} \times 100 \quad \text{---- Eqn. 2}$$

$$\text{Percentage yield (\%)} = \frac{\textit{Total microspheres weight}}{\textit{Total solid weight}} \times 100 \quad \text{---- Eqn. 3}$$

Particle size determination

Particle sizing experiments are generally carried out by means of particle size analyzers based on laser diffractometry. The particle size and distribution play a key role in the drug dissolution and other attributes of spray dried product and is one of the important parameters for characterization [32].

Thermal Characterization

Differential Scanning Calorimetry (DSC) analysis is useful in the investigation of thermal properties of the spray dried microspheres, providing both qualitative and quantitative information about the physicochemical state of drug inside the spray dried product. The comparison of melting endotherms of pure drug, taste masking polymer, physical mixture and spray dried microspheres is useful to understand the change in physical state of drug during entrapment in spray dried microspheres [27].

FTIR Analysis

FT-IR spectroscopy is useful in revealing the possibility of an interaction between drug and polymer in solid state. Structural changes and lack of crystal structure can lead to changes in bonding between functional group which can be detected by infrared spectroscopy [33].

Scanning Electron Microscopy:

The Scanning Electron Microscope (SEM) uses a focused beam of high-energy electrons to generate a variety of signals at the surface of solid specimens. The signals that derive from electron-sample interactions reveal information about the sample including external morphology (texture), chemical composition, and crystalline structure and orientation of materials making up the sample [34].

Taste evaluation study

The taste of spray dried product is generally evaluated by human panel studies in which the human volunteers rate the taste of pharmaceutical product according to its relative bitterness. In-vitro approach where the amount of drug released at salivary pH is compared to threshold value of bitterness is also employed as an alternative method for taste assessment [35]. Recently, electronic tongue has been used for evaluation of taste in pharmaceutical products. Sollohub *et al.*, evaluated the taste of spray dried roxithromycin using an electronic tongue which showed excellent taste masking efficiency of the developed microcapsules [36].

Table 1. Advantages of spray drying technique [12, 13]

Simple and rapid process
Control of particle size, shape, porosity and density
Reproducible and scalable
Require mild temperature conditions
Produces free flowing and spherical particles
Requires no additional processing before compaction into tablets
Enhanced dissolution rate of drugs
Cost effective

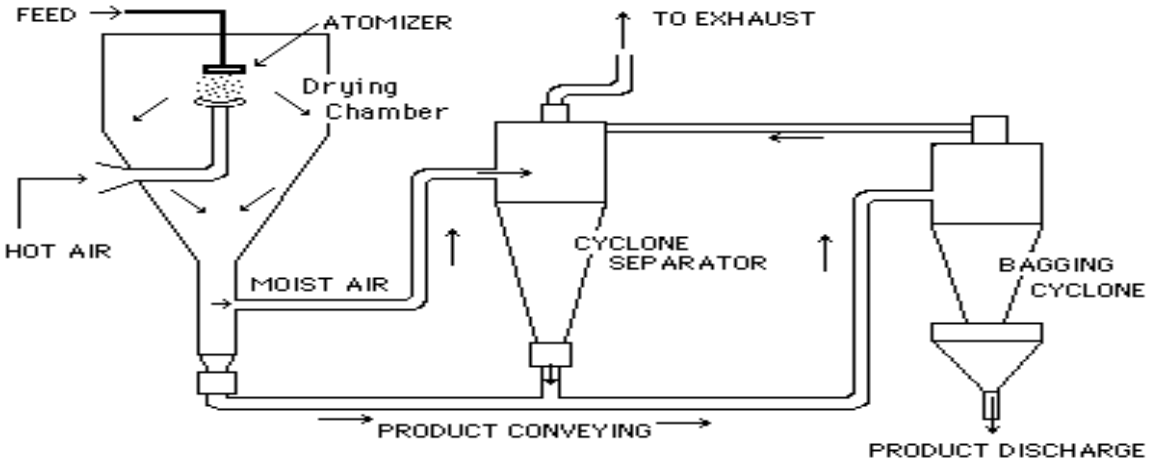

Figure 1: Components of spray dryer

CONCLUSION

Taste masking has gained lot of significance in pharmaceutical product development to improve patient compliance. New taste masking technologies to mask the bitter taste of drugs are now constantly being developed by the pharmaceutical and drug delivery companies. In the present review, the authors have presented spray drying as a viable and simple technique for taste masking of bitter drugs. The major highlight of this technique is that the taste is masked without interfering with the release of drug in gastric environment which make it very suitable technique for taste masking of immediate release dosage forms meant for oral administration. By carefully controlling the various factors, this technique can result in a pharmaceutical product with desired pharmaceutical characteristics and adaptability to various dosage forms. The multiple benefits offered by this technique will continue to appeal both academicians and pharmaceutical companies for pharmaceutical taste masking.

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