INVESTIGATION OF TASTE MASKING TECHNIQUES AND DEVELOPMENT OF DAPOXETINE HCL ORALLY DISINTEGRATING TABLET

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UNIVERSITI SAINS MALAYSIA

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by

LIEW KAI BIN

Thesis submitted in fulfillment of the requirement

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LIEW KAI BIN

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATION & SYMBOLS

˚C	Degree celsius
ρ	Density
ACN	Acetonitrile
ANOVA	Analysis of variance
API	Active pharmaceutical ingredient
As	Peak asymmetry factor
AUC	Area under curve
BCS	Biopharmaceutical Classification System
BP	British Pharmacopoeia
$CaCl_2$	Calcium chloride
$CaCO_3$	Calcium carbonate
cm	Centimetre
CO_2	Carbon dioxide
Cstd	Concentration of standard
CV	Coefficient of variation
CD	Cyclodextrin
CYP	Cytochrome P450
Dapoxetine HCl	Dapoxetine hydrochloride
DCP	Dicalcium phosphate
DSC	Differential Scanning Calorimetry
DT	Disintegration time
ED	Erectile dysfunction
FDA	Food and Drug Administration
Fig	Figure

FTIR	Fourier transform infrared spectroscopy
GI	Gastro-intestinal
GRAS	Generally regarded as safe
HCl	Hydrochloric acid
HPβ-CD	Hydroxypropyl beta-cyclodextrin
HPLC	High performance liquid chromatography
HPMC	Hydroxypropyl methyl cellulose
IELT	Intravaginal ejaculatory latency time
IS	Internal standard
ISSM	International Society for Sexual Medicine
k’	Capacity factor
KBr	Potassium bromide
KCl	Potassium chloride
KH_2PO_4	Potassium dihydrogen phosphate
LC-MS/MS	Liquid chromatography–tandem mass spectrometry
LLOQ	Lower Limit of quantification
LOD	Limit of detection
LOQ	Limit of quantification
LSR	Lubricant sensitivity ratio
MCC	Microcrystalline cellulose
MF	Matrix factor
MgCl	Magnesium chloride
MgSt	Magnesium strearate
N	Theoretical plates
NaCl	Sodium chloride

NaOH	Sodium hydroxide
NHDC	Neohesperidine dihydro chalcone
ODT	Orally disintegrating tablet
ODF	Orally disintegrating film
PE	Premature ejaculation
PEG	Polyethylene glycol
pKa	Acid dissociation constant
PVC	Polyvinyl chloride
PVP	Polyvinyl pyrolidone
QC	Quality control
RH	Relative humidity
r	Radius
R^2	Correlation coefficient
R&D	Research and development
rpm	Rotations per minute
RSD	Relative standard deviation
SD	Standard deviation
SEM	Scanning electron microscopy
SPSS	Statistical procedures for social science
SSRI	Selective serotonin reuptake inhibitor
T	Tailing factor
$T_{50\%}$	Time for 50% of drug release
ULOQ	Upper limit of quantification
USP	United States Pharmacopoeia
UV	Ultraviolet
VA	Vinylacetate

VP	Vinylpyrolidone
$W_{0.05}$	Width of peak at 5% height
XRD	X-ray diffraction
α	Alpha
β	Beta
β-CD	Beta-cyclodextrin

PENYIASATAN TEKNIK-TEKNIK PENUTUPAN RASA DAN PEMBANGUNAN TABLET TERKECAI ORAL DAPOXETINE HCL

ABSTRAK

Dalam pembangunan tablet terkecai oral (ODT), kesedapan memainkan peranan yang penting. Oleh kerana kajian mengenai penutupan rasa drug yang menyebabkan kepedihan mukosa mulut dan rasa pahit adalah amat jarang, dapoxetine HCl dipilih untuk kajian ini. Pelbagai teknik penutupan rasa telah dikaji termasuk pembentukan kompleks dengan resin penukaran ion, penyalutan dengan polimer sensitif pH, penyalutan dengan polimer hidrofilik, pengubahsuaian kimia, penambahan pemanis dan perisa, pembentukan kompleks inklusi dan penjerapan dengan sebatian bukan organik. Pembentukan kompleks dengan resin penukar ion (Kyron T-134) telah didapati sebagai teknik penutupan rasa terbaik dengan pembentukan kompleks drug-resin yang tidak larut di dalam rongga mulut. Dalam pembangunan ODT, pengeringanbekuan, acuan pelakuran, peralihan fasa dan teknik pemampatan langsung telah dikaji. Dalam teknik pengeringanbekuan, kesan polimer (hidroksipropil metilselulosa (HPMC), Carbopol 934P dan Eudragit® EPO) dan kanji gandum, ke atas sifat-sifat fizikal ODT dikaji. Peningkatan kepekatan polimer dan kanji gandum meningkatkan kekerasan dan masa pengecaian ODT. ODT yang terdiri daripada HPMC dan kanji gandum dengan kekerasan 0.86 ± 0.04 kg dan masa pengecaian in-vitro 166,67 ± 4.32 s telah diperolehi. Dalam teknik acuan pelakuran, mentega koko digunakan sebagai matriks. Penambahan PEG 6000 dan lilin lebah meningkatkan kekerasan dan masa pengecaian ODT. Sebaliknya, penambahan kanji jagung meningkatkan kekerasan tetapi mengurangkan masa pengecaian ODT.

Pengecaian yang cepat dicapai melalui peleburan matriks mentega koko dan pengembangan kanji jagung, yang mengganggu integriti matriks tablet. ODT yang mempunyai kekerasan dan masa pengecaian *in-vitro* 2.93 ± 0.22 kg dan 151.67 ± 6.98 s telah dihasilkan. Untuk teknik peralihan fasa pula, tiga gula alkohol bertakat lebur tinggi (mannitol, maltitol dan erythritol) dan takat lebur rendah (xylitol, trehalose dan sorbitol) telah dikaji. Gabungan mannitol dan trehalose didapati optimum dengan nilai kekerasan 8.81 ± 0.18 kg dan masa pengecaian in-vitro 167.17 ± 3.87 s. Takat lebur gula alkohol yang rendah bertindak sebagai pengikat meningkatkan keluasan permukaan ikatan antara zarah dan meningkatkan kekerasan ODT. Masa pengecaian in-vitro ODT yang dihasilkan dengan menggunakan tiga teknik yang dihuraikan adalah lebih kurang 3 minit. Pemampatan langsung adalah kaedah yang mudah, cepat dan lebih murah. Penggunaan adjuvan ko-pemprosesan yang boleh dimampat dengan sifat pengecaian cepat adalah salah satu cara untuk menangani cabaran teknik pemampatan langsung. Empat jenis "superdisintegrants" iaitu, natrium kanji glycolate, natrium croscarmellose, crospovidone XL-10 dan natrium polacrilin (Kyron T-314), telah dikaji. Gabungan Kyron T-314 (pengembangan) dan crospovidone XL-10 (kesan kapilari) didapati sebagai kombinasi yang optimum untuk mencapai pengecaian terpantas. Adjuvan ko-pemprosesan yang terdiri daripada natrium polacrilin (Kyron T-314), crospovidone XL-10, mannitol dan selulosa mikrokristalin, telah dihasilkan dengan menggunakan kaedah granulasi basah, dan digunakan untuk menghasilkan ODT penutupan rasa dapoxetine dengan kekerasan dan masa pengecaian 6.77 ± 0.38 kg dan 58.00 ± 3.85 s masing-masing. Kesimpulannya, pembentukan kompleks dengan resin penukaran ion (Kyron T-134) didapati teknik terbaik dan pemampatan langsung menggunakan adjuvan ko-pemprosesan yang terdiri daripada natrium polacrilin (Kyron T-314),

Crospovidone XL-10, mannitol dan mikrokristalin selulosa, adalah kaedah pembuatan yang diingini. Penemuan dalam penyelidikan ini boleh menyumbang kepada kemajuan penutupan rasa dan pembangunan formulasi ODT.

INVESTIGATION OF TASTE MASKING TECHNIQUES AND DEVELOPMENT OF DAPOXETINE HCL ORALLY DISINTEGRATING TABLET

ABSTRACT

In the development of orally disintegrating tablets (ODT), palatability plays a critical role. As there were hardly any reported studies on taste masking of drugs which cause burning sensation on oral mucosa and is bitter in taste, dapoxetine HCl was chosen for the study. Various taste masking techniques, namely complex formation with ion exchange resin, coating with pH sensitive polymer, coating with hydrophilic polymer, chemical modification, addition of sweetener and flavour, inclusion complexation and blending with inorganic compound, were investigated. Complex formation with ion exchange resin (Kyron T-134) was found to be the best taste masking technique by formation of insoluble drug-resin complex in the oral cavity. In the development of ODT, lyophilisation, fusion moulding, phase transition and direct compression techniques were investigated. In the lyophilisation technique, the effect of polymers (hydroxypropyl methylcellulose (HPMC), Carbopol 934P and Eudragit® EPO) and wheat starch, on the physical properties of lyophilized ODT was studied. Increasing the concentration of polymers and starch increased the hardness and disintegration time of ODT. ODT comprising HPMC and starch with hardness of 0.86 ± 0.04 kg and *in-vitro* disintegration time of 166.67 ± 4.32 s was obtained. In the fusion moulding technique, cocoa butter was used as the matrix. Addition of PEG 6000 and beeswax increased the hardness and disintegration time of ODT. On the other hand, addition of corn starch increased the hardness but reduced the

disintegration time of ODT. Faster disintegration was achieved through melting of cocoa butter and swelling of corn starch, leading to the disruption of tablet integrity. The ODT tablet with hardness and *in-vitro* disintegration time of 2.93 ± 0.22 kg and 151.67 ± 6.98 s was produced. For phase transition technique, three high melting point (mannitol, maltitol and erythritol) and low melting point (xylitol, trehalose and sorbitol) sugar alcohols were studied. The combination of mannitol and trehalose was found to be optimum with hardness value of 8.81 ± 0.18 kg and *in-vitro* disintegration time of 167.17 ± 3.87 s. The low melting point sugar alcohol acted as binder increasing the bonding surface area between particles, enhancing the hardness of ODT. The *in-vitro* disintegration time of the ODT produced using the three techniques was approximately 3 min. Direct compression is a relatively simple, rapid and more economical method. The use of co-processed adjuvant that was compressible with fast disintegration characteristic was one of the means to circumvent the challenges of direct compression technique. Four types of superdisintegrants namely, sodium starch glycolate, croscarmellose sodium, Crospovidone XL-10 and polacrilin potassium (Kyron T-314), were studied. Combination of Kyron T-314 (swelling) and crospovidone XL-10 (wicking) was found as the optimum combination to achieve the fastest disintegration. Co-processed adjuvant consisting of polacrilin potassium (Kyron T-314), Crospovidone XL-10, mannitol and microcrystalline cellulose, was prepared using wet granulation method, and used to produce taste masked dapoxetine ODT with hardness and *in-vitro* disintegration time of 6.77 ± 0.38 kg and 58.00 ± 3.85 s. In conclusion, complex formation with ion exchange resin (Kyron T-134) was found to be the best taste masking technique and direct compression using a newly developed co-processed adjuvant consisting of polacrilin potassium (Kyron T-314), Crospovidone

XL-10, mannitol and microcrystalline cellulose, was the preferred manufacturing method. The findings in this current research could contribute to the advancement in taste masking and ODT formulation development.

CHAPTER 1

INTRODUCTION

1.1 Background of orally disintegrating tablet

Oral drug delivery remains the most popular route of drug delivery (Sudhir *et al*., 2010). It is because oral drug delivery system has the key advantage of convenient administration. Tablets and hard gelatin capsules constitute a major portion of drug delivery systems that are currently available due to its convenience of self administration, compactness and simple manufacturing process. Moreover, drug is found to be more stable in solid dosage form than liquid dosage form. However, many patients experience the fear of swallowing tablets and capsules. Some patients have experienced choking while taking tablets or capsules of large size. As a result, they do not take their medication as prescribed and non-compliance issues arise. Honda and Nakano (1998) conducted a survey and found that half of patients experienced difficulty in taking solid medications such as tablets and capsules, which resulted in a high incidence of non-compliance and ineffective therapy. Majority of patients who are found to be non-compliant to the treatment are paediatric and geriatric populations (Seager, 1998). The mentally retarded and un-cooperative, nauseated or on reduced liquid-intake/diet patients, have difficulties swallowing these dosage forms. Patients who travel or have little access to water are similarly affected (Hanawa *et al.*, 1995).

Orally disintegrating tablets (ODTs) are also known as orodispersible tablets, mouth dissolving tablets, fast melt tablets, rapid dissolving tablets and quick dissolving tablets (Hirani *et al*., 2009). ODT systems came into existence in the

late 1970's as an alternative to tablets and capsules for pediatric and geriatric patients who experience difficulties in swallowing traditional oral solid dosage forms (Hanawa *et al*., 1995).

Orally disintegrating tablets (ODT) are different from chewable tablets and effervescent tablets. Chewable tablets are not practical for patients suffering from mouth ulcer or have difficulty in chewing or painful oral cavity. On the other hand, effervescent tablet requires water to dissolve the tablet which might not be available in some situations such as during traveling (Mizumoto *et al*., 2005).

Bradoo (2001) listed a few ideal characteristics that ODTs should have. The ODT should

a. disintegrate in mouth in a matter of seconds.
b. be taken directly without requires the access to water due to its fast disintegrating property.
c. employ effective taste masking technique.
d. have pleasant mouth feel.
e. be robust and less friable.
f. be stable.
g. have simple manufacturing method which can use conventional processing and packaging equipment.
h. allow high drug loading.
i. be cost effective.

Kuchekar *et al*. (2003) listed some of the advantages of ODTs over other dosage forms:

a. ODT is a patient friendly dosage form; it reduces the risk of choking and eliminates the fear of swallowing tablets.
b. convenient in administration as water access is not a must.
c. accurate and precise dosing as compared to liquids.
d. rapid disintegration of the dosage form that speeds up the dissolution of drug and absorption, leading to rapid onset of pharmacological action.
e. convenient for administration and improved patient compliance especially for geriatric, pediatric, disabled and bedridden patients.

1.2 Patient's preference

Patient preference is an important factor in long-term treatment adherence and thus treatment outcome (Jahng *et al*., 2005). A survey revealed that almost half of the patients prefer ODTs to other dosage forms (Deepak, 2004) and about 70% respondents would ask their doctors for ODTs if they are given a choice. Around 70% patients would choose to purchase ODT products and 80% respondents indicated that they prefer ODT products than regular tablet or liquid dosage forms (Brown, 2003). There was another survey carried out by Kinon *et al* (2003) on the preference of patients on olanzapine ODT and conventional tablet using the Patient Global Impression Scale (1- I like it very much; 7 - I dislike it very much). The average score for the ODT product was in the range of 2.01 – 2.74, signifying a positive acceptance of the product at all measured time points. Bitter *et al.* (2010) investigated the preference of patients on oral olanzapine formulation by

comparing patients' preference for ODT versus conventional tablet in a randomized open-label crossover study. Overall, 61% of patients preferred ODT and only 27% preferred conventional tablets while 12% expressed no preference.

1.3 Problem statement

ODT is a novel oral drug delivery system which offers added advantages over conventional dosage forms such as ease of administration, elimination of fear of choking and faster pharmacological onset. However, there are certain challenges in the development of ODT, which include rapid and cost effective processing method, satisfactory palatability, rapid disintegration time, and stability. The ODT inventions in the market disintegrate mainly through porous and weak tablet matrix, swelling and wicking of disintegrant. The mechanical strength and hardness of ODT are often compromised to achieve rapid disintegration. Special packaging is needed to protect the product integrity which results in an increase in overall production cost.

Dapoxetine HCl is a drug candidate which causes burning sensation on oral mucosa and is bitter in taste. Up-to-date, there is hardly any study on taste masking techniques for drugs causing burning sensation on oral mucosa. As such, present research could generate new knowledge in the field of orally disintegrating drug delivery systems.

Dapoxetine HCl in the form of ODT has not yet been available commercially. Dapoxetine HCl ODT could serve as a convenient and patient friendly dosage form.

Effective taste masking techniques to improve palatability of drug candidate causing burning sensation in oral cavity and amicable manufacturing methods of ODT are crucial to contribute to the success of ODT.

1.4 Experimental work and scope of study

The study was performed in various stages encompassing the following objectives:

1. To investigate the various taste masking techniques to improve the palatability of dapoxetine HCl
2. To develop orally disintegrating tablets using
    a. lyophilization technique and investigation of the effects of polymers and starch on the physical properties of lyophilized ODT
    b. fusion moulding technique and investigation of the effects of waxes, starch and PEG 6000 on the development of cocoa butter based ODT
    c. phase transition technique and characterization of ODT
    d. direct compression technique and development of novel co-processed adjuvant
3. To develop and validate bioanalytical LC-MSMS assay method to quantify dapoxetine in plasma sample.

CHAPTER 2

LITERATURE REVIEW

2.1 Taste masking

Taste refers to a perception arising from the stimulation of taste buds present on the surface of the tongue. Humans can distinguish the components of taste: sourness, saltiness, sweetness and bitterness (Ayenew *et al*., 2009). Taste masking technology is used in development of orally disintegrating dosage forms, as majority of drugs are bitter in nature. When the dosage form disintegrates in the mouth, the taste bud is exposed to the bitter drug.

Hitherto, various taste masking technologies have been developed to address the problem of patient compliance. Below is the summary of some taste masking technologies used in the formulation of orally disintegrating dosage forms.

2.1.1 Taste masking strategies

Most of the active pharmaceutical ingredients have poor taste and bad mouth feel. Some might even cause irritation and burning sensation on the tongue. Effective taste masking strategies are required to formulate a good orally disintegrating dosage form.

2.1.1(a) Coating

Coating is suitable for very bitter drug molecules. It is an efficient way to prevent the bitter molecules from being in direct contact with the taste buds. Hydrophobic polymers, lipids, sweeteners and hydrophilic polymers are common coating

materials. Roche *et al*. (1993) reported taste masked famotidine formulated using a combination of water soluble polymer (polyvinylpyrrolidone) and water insoluble polymer (cellulose acetate) as the coating material. Yeong *et al*. (2003) described the wet granulation of a mixture of pivoxil sulbactam and stearic acid with ethanolic solution of polyvinylpyrrolidone, followed by coating with colloidal silicon dioxide in a high speed rotary mixer to achieve taste masking. Granules containing ibuprofen, polyvinylpyrrolidone, sodium starch glycolate and sodium lauryl sulphate, were coated with hydroxyethyl cellulose and a mixture of hydroxyethyl cellulose and hydroxypropyl methylcellulose, to achieve taste masking. However, coating of drugs might retard the dissolution process in certain cases. Choosing the appropriate coating material is important so that the new formulation is bioequivalent with the original formulation (Fu *et al*., 2004).

2.1.1(b) Granulation

It is an economical, practical and rapid process, which most industries are affordable to apply. Wet granulation can be used to mask the bitter taste of drugs. Granulation can be formed by mixing the bitter medicament, with sweeteners, hydrophobic polymers, lipids or waxes.

Liquid and low melting point waxes such as glycerol palmitostearate, glyceryl behenate and hydrogenated castor oil are commonly used ingredients during the granulation to achieve taste masking (Ayenew *et al*., 2009).

Bertelsen *et al.* (2006) described the melt granulation to achieve the taste masking of calcium carbonate. The method involved a melt granulation process where a

sugar alcohol was melted in which calcium-containing compound was embedded to mask the chalkiness and unpleasant mouth feel of the calcium-containing compound.

2.1.1(c) Addition of sweetener and flavor

This is a simple taste masking method that can be used alone or in combination with other strategies to achieve better taste masking. The use of synthetic sweeteners such as saccharine sodium, aspartame and sucralose are common in most taste masked products. Although artificial sweeteners have an intense sweetness, they leave a bitter or metallic after taste, which cause non-compliance in patients. To solve this problem, artificial sweeteners were used in combination with sugar alcohols such as lactitol, maltitol and sorbitol, to decrease the after-taste of artificial sweeteners. Sucralose can be used with physiologically acceptable acids (e.g. citric acid) to increase the taste masking efficiency of the sweetener. More recently, newer sweeteners derived from plant parts have been evaluated for taste masking efficiency. For example, stevia was used to prepare taste masked ibuprofen (Roche *et al*., 1993). Ammonium glycyrrhizinate which is extracted from glycyrrhiza root and is 50-60 times sweeter than sucrose is used in the food industry (Couteau and Coiffard, 2001).

2.1.1(d) Microencapsulation

Microencapsulation is a process by which very tiny droplets or particles of liquid or solid material are surrounded or coated with a film or polymeric material (Sharma and Lewis, 2010).

Advantages

• Taste masking can be achieved with the desirable controlled drug release.

• Bitter liquids may be coated to convert them to solid particles.

•The coated bitter particles can adapt to a wide variety of dosage forms and product applications.

The goal of microencapsulation may be accomplished by any of the following techniques:

• Air suspension coating

• Coacervation-phase separation

• Spray drying and spray congealing

• Solvent evaporation

• Multiorifice-centrifugal process

• Pan coating

• Interfacial polymerisation

Some of the publications are given in Table 2.1:

Table 2.1: Taste masking by microencapsulation techniques reported in literature.

Authors	Technique	Microencapsulation coating agent	Drug	Dosage form
Seager (1977)	Spray drying	Sodium CMC	Ampicillin trihydrate	Powder
Bhardwaj and Hayward (1996)	Wurster fluid bed coating	Eudragit RL 30D, RS30D	Caffeine, Cimetidine	Chewable tablet
Yajima *et al*. (1996)	Spray congealing	Glyceryl monostearate, Eudragit E100	Clarithromycin	Powder
Hoy and Roche (1996)	Tangential spray fluid bed coating	Eudragit E-100; Cellulose acetate	Acetaminophen	Chewable tablet
Mauger and Robinson (1998)	Solvent Evaporation	Eudragit E, Fattibase	Metronidazole	Dry Suspension
Iton and Niwa (2001)	Top spray fluid bed coating	Eudragit NE30D, E-100	Sildenafil citrate	Mouth melt tablet

2.1.1(e) Taste suppressant and potentiator

Bitter blockers such as adenosine monophosphate are a group of compounds which compete with bitter substances to bind with G-protein coupled receptor (GPCR) sites (Margolskee and Ming, 2003). In general, binding of the bitter substance to the receptor causes the sensation of bitterness on the tongue. Lipoproteins are universal bitter taste blockers. Venkatesh and Palepu (2002) described the application of taste suppressants like phospholipid (BMI-60) in taste masking of bitter medicaments. Potentiators increase the perception of the taste of sweeteners and mask the unpleasant taste. Various potentiators include thaumatin, neohesperidine dihydro chalcone (NHDC) and glycyrrhizin can increase the

perception of sodium or calcium saccharinates, saccharin, acesulfame and cyclamates (Abraham and Mathew, 2014). The various taste suppressants and potentiators used for taste masking reported by other researchers are presented in Table 2.2.

Table 2.2: Taste masking by taste suppressant / potentiator reported in literature.

Drug	**Category**	**Taste suppressant/potentiator used**	**Reference**
Bromhexine	Mucolytic	Thaumatin and sugar	Scheuring *et al*., 2013
Caffeine	Diuretic	Hydroxyflavones	Ley *et al.*, 2012
Caffeine	Diuretic	Gamma-amino butyric acid	Kardos and Blandl, 1994
Paracetamol	Antipyretic	Potentiators: glycyrrhizin, thaumatin, and neohesperidine dihydro chalcone Sweeteners: Saccharin salts, acesulfame	Abraham and Matthew, 2014

2.1.1(f) Ion exchange resin

Ion exchange resins can be used as a method to mask the taste of a bitter molecule. They are high molecular weight polymers with cationic and anionic functional groups. Sudhakar *et al*. (2007) reported a method using polacrilin resin (porous copolymer of methacrylic acid crosslinked with divinyl benzene) to mask bitter taste of drugs such as cetirizine dihydrochloride and levocetirizine. A wet granular mass of drug with cationic resin was prepared. The dried granules were mixed with mannitol, crospovidone, microcrystalline cellulose and magnesium

stearate to form directly compressed chewable tablets. Bess *et al*. (2010) used ion exchange resin (Amberlite) to formulate taste masked dextromethorphan ODF.

2.1.1(g) Inclusion complexation

Cyclodextrins have been proposed as a taste masking agent in orally disintegrating dosage forms. Inclusion complexation is a process in which the drug molecule fits into the cavity of cyclodextrin. Cyclodextrin is capable of masking the bitter taste of the drug by decreasing the number of drug particles exposed to the taste buds, thereby reducing the perception of bitter taste (Nilesh *et al*., 2012).

2.1.1(h) Adsorption

Adsorbates can be used as taste masking agent. Drug solution can be mixed with an insoluble substrate that adsorbs on the surface of the drug particles when the solvent is removed. Substrates like Veegum®, bentonite, silica gel and silicates can be used for the preparation of adsorbate of bitter drugs (Sharma and Lewis, 2010).

2.1.1(i) Gelation

Sodium alginate has the ability to form water insoluble gelation on the surface of tablet in the presence of bivalent metal ions and can be used for taste masking of bitter drug. Tablet of amiprolose hydrochloride has been taste masked by applying an undercoat of sodium alginate and overcoat of calcium gluconate. In the presence of saliva, sodium alginate reacted with bivalent calcium to form a water insoluble gel for taste masking (Kaneko *et al.*, 1997).

2.1.1(j) Effervescent agents

Effervescent agents, mixtures of sodium bicarbonate and organic acids, can be used as taste masking agents for solid dosage forms. The formulation contains the drug in combination with effervescent agent to promote their absorption in the oral cavity and to mask their bitter taste (Pather *et al*., 2002).

2.2 Challenges in development of ODT

Developing and manufacturing of ODT has never been an easy task. Habib *et al*. (2000) listed some potential challenges in developing ODT formulations.

2.2.1 Mechanical strength and disintegration time

ODTs are made of either very porous tablet structure or compressed into tablets with very low compression force for rapid disintegration in the oral cavity. As a result, the ODTs are friable, brittle, difficult to handle, and often require specialized peel-off blister pack to protect the product. Such fragile tablets tend to break during packing, transporting or handling by patients. Increasing the mechanical strength could adversely delay the disintegration time of the ODTs.

2.2.2 Palatability and taste masking

Many drugs are bitter in taste. It is not acceptable if ODT disintegrates and the bitter drugs dissolve in saliva to leave a bad taste. Poor taste will seriously affect patient compliance and acceptance of the dosage form. Effective taste masking technique which can mask the bitter taste of the drugs must be used so that the taste of the drug is not felt in the oral cavity. ODT with good taste increases the acceptance of patients and hence resolves the non-compliance issue. Mouthfeel is

another critical factor which affects the acceptance of the dosage form. ODT which disintegrates into larger particles in the oral cavity leave a poor mouthfeel on the tongue. The particles generated after disintegration of the ODT should be as small as possible. The addition of flavours and cooling agents, such as menthol, improves the mouth feel.

2.2.3 Physical stability

Most of the ODTs are hygroscopic in nature due to the ingredient used in the formulation and cannot maintain physical integrity under normal condition of temperature and relative humidity. Hence, special packaging is needed to protect the product from humidity.

2.2.4 Cost of production

ODT that is packed in specialized packaging increases the production cost. Similarly, ODTs for example, Zydis and Orasolv, that require special technologies and equipment, increase the cost of production to a remarkable extent (Habib *et al*., 2000).

2.2.5 Drug loading

The drug loading capacity determines whether a dosage form is practical. High drug loading capacity is generally desired. Incorporation of high dose of drug in ODT is very challenging as it can adversely affect the physical property of ODT especially the disintegration time. For lyophilized dosage forms, the dose should be less than 400 mg for insoluble drugs and less than 60 mg for soluble drugs (Ghosh and Pfister, 2005).

2.3 Approaches in ODT development

ODT development employs one of the following approaches to achieve fast disintegration: maximizing the porous structure of the tablet matrix, incorporating appropriate disintegrating agent or using highly water-soluble excipients in the formulation (Kaur *et al*., 2011).

2.3.1 Freeze-drying

This method is suitable for thermolabile drugs since it does not employ heat in the manufacturing process. It is a process in which water is sublimated from the product after freezing. In this method, the active ingredient is first dissolved or dispersed in a polymeric / carrier solution. The solution / dispersion is then casted by weight into blister packs / moulds. The trays holding the blister packs / moulds are stored in freezer for freezing and the freeze drying process is continued with a freeze dryer. Finally, the blisters are packaged and shipped. The product prepared using this method is highly porous and has a very high specific surface area, which dissolves rapidly when in contact with water (Makino *et al*., 1996; Seager, 1998; Reddy *et al*., 2002). The disadvantages of this method besides fragile product, are the high cost of equipment and complex processing steps (Kaur *et al*., 2011). Fig. 2.1 shows the picture of an industrial freeze drying machine.

Fig 2.1: Cuddon FD 1000 freeze dryer (adapted from http://www.foodprocessing-technology.com/contractors/freezers/cuddon/cuddon5.html).

2.3.2 Tablet moulding

Tablet moulding method uses water-soluble ingredients so that the tablets dissolve completely and rapidly. Moulding process includes moistening, dissolving, or dispersing of drug with a solvent. The powder blend is then moulded into tablets under pressure lower than that used in conventional tablet compression. Air drying process removes the solvent in the tablet. As a result, moulded tablets are very porous and less compact than compressed tablets. The ODT possesses porous structure that improves dissolution (Dobetti, 2001; Reddy *et al*., 2002). However, the low hardness of the moulded tablets might be the limitation of this technique. Therefore, binding agents are required as part of the formulation to increase the mechanical strength of the tablets. Masaki and Ban (1995) reported the use of agar solution as binding agent in the preparation of an intrabuccally fast disintegrating tablet. This method is more practical to scale up for industrial manufacture than the lyophillization technique.

2.3.3 Compression-sublimation

Sublimation is a manufacturing method which produces porous ODT with fast disintegration. Inert solid ingredients that volatilize readily (e.g. urea, ammonium carbonate, ammonium bicarbonate and camphor) are mixed with other tablet ingredients and the mixture is compressed into tablets. The volatile materials were then removed through sublimation by heat, producing ODT with porous structure (Makino *et al*., 1996). Koizumi *et al*. (1997) developed ODT using camphor as subliming material. Camphor was sublimated in vacuum at 80^0C for 30 min after preparation of ODT tablets. The ODTs produced disintegrated within 15 sec.

2.3.4 Spray drying

Allen and Wang (1996) reported a process for making a particulate support matrix for producing a rapidly dissolving tablet. Hydrolyzed and non-hydrolyzed gelatin were used as supporting matrix, mannitol as bulking agent, sodium starch glycolate as superdisintegrant, citric acid as buffering agent, water and ethanol as solvent system. The composition was introduced into the spray drying chamber. The particle formed from the droplet retained a high porosity and low density. The particulate support matrix could then be mixed with drug, flavouring agent, and a small amount of effervescent material (optional) to produce a rapidly dissolving tablet by one of the manufacturing methods such as direct compression.

2.3.5 Mass extrusion

Mass extrusion involves softening of the active blend using a solvent mixture of water-soluble polyethylene glycol and methanol, subsequent expulsion of

softened mass through the extruder into well-formed cylindrical extrudates, and cut into even segment using heating blade (Reddy *et al*., 2002).

2.3.6 Compression-phase transition technique

Kuno *et al*. (2008) introduced compression-phase transition technique to produce ODTs. This method was dependent upon the melting point of sugar alcohols. The process involved compressing the powder containing two sugar alcohols of high and low melting points and subsequently heating the compressed mass at the temperature between their melting points. Before the heating process, tablet did not have sufficient hardness because of the low compactability. However, tablet hardness was found to increase after heating due to diffusion and solidification of sugar alcohols (Kuno *et al*., 2008).

2.3.7 Direct compression technique

Direct compression is the easiest and conventional way to manufacture ODT. The advantages of this method are low manufacturing cost, the use of conventional equipment and a few processing steps. However, the disintegration and dissolution of the ODT are slower due to the more compacted and less porous ODT formed. The disintegration of ODT manufactured using this method relied on superdisintegrant, water soluble excipients and effervescent agents (Makino *et al*., 1996; Reddy *et al*., 2002).

The survey conducted by Shangraw and Damarest (1993) showed that direct compression was the most preferred tablet manufacturing method compared to wet granulation and roller compaction. About 41% of the surveyed companies

responded that direct compression was the method of choice, 41.1% indicated that they used both direct compression and wet granulation method. Only 1.7% indicated that they never used direct compression method and 15.5% indicated that the process was not recommended.

This method is simple and rapid compared to the more complicated and long process involved in the manufacture of tablets by wet granulation and roller compaction (Shangraw, 1989). It requires less equipment, lower power consumption, less space, less time and less labour leading to reduced production cost. Moreover, this method is suitable for moisture and heat sensitive APIs since the method does not involve wetting and drying of ingredients (Patel and Bhavsar, 2009).

However, the limitation is that not every single pharmaceutical excipient is suitable for direct compression. It has been estimated that less than 20% of pharmaceutical materials have high compressibility and can be compressed directly into tablets (Shangraw, 1989). Most of the pharmaceutical excipients lack the flow, cohesion or lubricating properties necessary for the production of tablets by direct compression. Weight variation and content uniformity problems might occur if the materials used lack of flowability.

2.3.8 Nanocrystal technology

The main principle behind nanocrystal technology is reduction of the particle size which results in increase of surface area, which in turn leads to an increase in dissolution. Nanocrystal colloidal dispersions of drug substance are combined

with water-soluble GRAS (Generally Regarded as Safe) ingredients (http://www.fda.gov/Food/IngredientsPackagingLabeling/GRAS/) filled into blisters and lyophilized. The resultant ODTs are remarkably robust and can dissolve in a very small quantity of water within seconds. This technique is especially suitable for production of highly potent or hazardous drug products because it removes the need for some manufacturing operations such as granulation, blending, and tableting, which might generate large quantities of aerosolized powder and present higher risk of exposure (Hirani *et al.*, 2009).

2.3.9 Cotton candy process-compression

This process utilizes a unique spinning mechanism to produce floss-like crystalline structure. Cotton candy process involves formation of matrix of polysaccharides or saccharides by simultaneous action of flash melting and spinning. The matrix formed is partially recrystallized to improve flow property and compressibility. This candy floss matrix is then milled and blended with active ingredients and excipients and subsequent compressed to orally disintegrating tablet. This process can accommodate larger drug doses and offers improved mechanical strength (Chiver and Minn, 1972).

2.4 Examples of patented ODT technologies

2.4.1 Zydis®

Zydis® is one of the oldest and best known technologies which use freeze-drying process to prepare ODT (Virely and Yarhood, 1989; Konar and Mukhopadhyay, 2014). The tablet dissolves in the mouth within seconds after placement on the tongue due to the highly porous structure of the tablet. As Zydis® dosage form is weak in physical strength, the tablet is contained in peelable blister pack, which allows product removal without damage (Ahmed *et al.*, 2006).

2.4.2 OraSolv®

CIMA Labs patented OraSolv® as its first ODT technology. OraSolv® uses effervescent principles to prepare ODT. The ODT contains effervescent material as disintegrating agent. The active ingredient is taste-masked beforehand. The ODT disintegrates very fast when the effervescent material dissolves in saliva. Carbon dioxide is generated by a reaction of the formulation components upon exposure to saliva in the mouth. Tablets are made by direct compression technique at low compression force to minimize oral dissolution time. OraSolv® usually dissolves in the oral cavity within 15 s to 3 min. Due to the low mechanical strength property, the ODT produced are soft and friable and packaged in specially designed pack (Tagaki *et al*., 2007).

2.4.3 DuraSolv®

CIMA Labs patented DuraSolv® as its second ODT technology. DuraSolv technology showed improvement in mechanical strength, which is the major limitation of Orasolv® . The DuraSolv® technology has a formulation similar to the OraSolv® technology, combining taste masked drug particles with or without a low amount of effervescent agent containing formulation. The tablets made by this technology consist of drug, fillers and a lubricant. Tablets are prepared using conventional tableting equipment and have good rigidity. Durasolv® technology has been developed for drug strengths in the range of 125 µg – 500 mg with disintegration times designed in the range of 10 to 50 seconds. With DuraSolv® technology, tablets are compressed to a greater hardness of 15 – 100 N, resulting in a more durable ODT. Durasolv® product is very robust and can be packed in traditional blister pack (Cirri *et al*., 2005).

2.4.4 Wowtab® technology

Wowtab® technology was patented by Yamanouchi Pharmaceutical Co (Fu *et al*., 2004). This technology utilizes sugar and sugar-like excipients. Two different types of saccharides are combined to produce fast dissolving tablets using conventional granulation and tableting technique. According to the patent, saccharides were divided into two groups, high mouldability and low mouldability. The low mouldability saccharides produced tablets with hardness between 0-2 kg when 150 mg of such saccharide was compressed under pressure of 10-50 kg/cm using a die of 8 mm in diameter. The typical low mouldability saccharides include lactose, mannitol, glucose, sucrose and xylitol for rapid dissolution. High mouldability saccharides produce tablets with hardness above 2 kg when prepared under identical conditions. The typical high mouldability saccharides are maltose, maltitol, sorbitol and oligosaccharides for good binding property. Saccharides having low mouldability were granulated with saccharides having high mouldability. The low mouldability saccharides were used as the main component. The Wowtab® formulation is more stable than Zydis® and OraSolv®.

2.4.5 Pharmaburst™ 500

SPI Pharma patented its ODT technology called Pharmaburst™ 500 (Kathpalia and Jogi, 2014). It utilizes co-processed excipients to develop ODT, which dissolves within 30-40 s. Pharmaburst™ 500 is a co-processed excipient which consists of mannitol, sorbitol, crospovidone, silica, aspartame and magnesium stearate. Pharmaburst™ 500 is a ready to use system which has been specifically engineered to manufacture robust, rapidly disintegrating ODTs with superior

organoleptic properties. Pharmaburst™ 500 can be used on standard tableting equipment to formulate tablets with up to 500 mg active ingredient.

2.4.6 Nanomelt™

Nanomelt™ employs nanocrystal technology to manufacture ODT. It was patented by Elan Corporation. Nanosized particles increases the surface area, which leads to a faster disintegration rate of tablet and an increase in dissolution rate. NanoCrystal™ particles are ultra-small particles which are typically less than 1000 nm in diameter. They are produced by milling the drug substance using a proprietary wet milling technique. Badgujar and Mundada (2011) provided the benefits of this technology which are given below:

a. Pharmacokinetic benefits of orally administered nanoparticles (less than 2 microns) in the form of a rapidly disintegrating tablet matrix.
b. Product differentiation based upon a combination of proprietary and patent-protected technology elements
c. Exceptional durability, enabling use of conventional packaging equipment and formats
d. Wide range of doses (up to 200 mg of active pharmaceutical ingredient per unit)
e. Use of conventional, compendia inactive components
f. Employment of non-moisture sensitive excipient

2.4.7 Flashdose® technology

Flashdose® technology was invented by Fuisz Technologies, USA. This technology utilizes the concept of cotton candy process. Fuisz Technologies has

developed three oral drug delivery systems that involve fast dissolution. The first two generations are quick-dissolving Soft Chew and EZ Chew tablets which require some chewing. Flashdose® technology is the third generation technology which uses a unique spinning mechanism to produce a flash-like crystalline structure, much like cotton candy. APIs can be mixed with these crystalline sugars and compressed into tablets. The floss cotton candy-like fibers are made up of saccharides such as sucrose, dextrose, lactose and fructose. Sucrose requires a temperature of 82–130 ℃ to be transformed into fibers while other polysaccharides such as polymaltodextrins and polydextrose require 30–40 % lower temperature than sucrose. The Flashdose® manufacturing process can be divided into four steps, (i) floss blend, (ii) floss processing, (iii) floss chopping and conditioning and (iv) tablet blend and compression (Fuisz, 1997; Badgujar and Mundada, 2011).

2.4.8 Flashtab®

Flashtab® technology was developed by Prographarm. In this technology, the disintegration depends on the combination of a disintegrating agent and a swelling agent. The coated taste-masked drug is blended with disintegrating agent and swelling agent by wet or dry granulation method followed by compression into tablets. The product is a compacted tablet with fast disintegration property. The packaging material is usually blister packed using high quality polyvinyl chloride or aluminum foil for providing a higher degree of moisture protection (Wagh *et al*., 2010).