DEVELOPMENT AND EVALUATION OF TASTE MASKED ORALLY DISINTEGRATING TABLETS OF A WATER SOLUBLE DRUG, SUMATRIPTAN SUCCINATE AND A WATER INSOLUBLE DRUG, ONDANSETRON

by

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Thesis submitted in fulfillment of the requirement for the degree of Doctor of Philosophy

December 2010

This thesis is dedicated to …..

My family members for their love, support and encouragement

and

To the Almighty

ACKNOWLEDGEMENTS

The successful completion of this research work has been possible largely due to invaluable assistance extended to me from many people to whom I would like to express my profound gratitude here.

I am highly grateful to my main supervisor Assoc. Prof. Dr. Yusrida Darwis for the invaluable guidance and support she has extended to me towards the realization of this work. I feel privileged to have the opportunity for working in her laboratory and I have immensely benefited. I also appreciate her kindness, encouragement, suggestions and in sharing knowledge and experience that made it possible to accomplish this research work.

I am very grateful to my co-supervisor Dr. Nurzalina Abdul Karim Khan for her overall support. Her invaluable advice, constructive criticism, suggestions and lively discussions helped me immensely to overcome all challenges in my research.

I would like to express my sincere thanks to Assoc. Prof. Dr. Syed Azhar Syed Sulaiman, Dean of School of Pharmaceutical Sciences for providing me the opportunity and facilities which made my study possible in the School of Pharmaceutical Sciences, Universiti Sains Malaysia.

I would like to express my heartfelt gratitude to the Institute of Postgraduate Studies for granting me USM Fellowship during my candidature.

Special thanks are also expressed to Mrs. Nurmaliza, Doping Control Centre, Universiti Sains Malaysia for her invaluable help in analysis of the samples by Gas Chromatography.

My sincere thanks are also expressed to Mr. Ali Zaini Hassan, laboratory technician in School of Chemical Sciences, Universiti Sains Malaysia for his invaluable help in providing assistance to utilize the spray dryer instrument.

I wish to thank the following laboratory staff in School of Pharmaceutical Sciences, Samsudin Bakar, Rahim Abdullah, Abdullah Ibrahim, Abdul Malek Mustafa, Mohd. Rizal, Yusuff Md. Saud and Roseli Hassan for their friendship, support and help during the period of my study.

I am grateful to all my friends and well wishers especially to Venkatesh, Rammohan, Mallikarjun, Rahamathullah, Raghu Raj Singh and Annegowda for their help, moral support and sharing their ideas and experiences in both science and life during my stay in Penang, Malaysia.

Last but not the least, I am most grateful and remain enormously indebted to my family for their love, support, encouragement and understanding during my research work.

Sheshala Ravi

TABLE OF CONTENTS

CHAPTER 5: DEVELOPMENT AND VALIDATION OF RP-HPLC-UV METHOD FOR THE DETERMINATION OF ONDANSETRON IN RABBIT PLASMA

LIST OF TABLES

LIST OF FIGURES

LIST OF PLATES

LIST OF ABBREVIATION & SYMBOLS

ºC	=	Degree centigrade
5-HT	=	5-Hydroxy-Tryptamine
ANOVA	=	Analysis of Variance
AUC	=	Area Under Curve
CCS	=	Croscarmellose Sodium
C_{max}	=	Maximum plasma drug concentration
CN	=	Cyano
DE	=	Dissolution Efficiency
DSC	=	Differential Scanning Calorimetry
HPLC	=	High Performance Liquid Chromatography
HPMC	=	Hydroxypropyl Methyl Cellulose
Hr	=	Hour
HSD	=	Honestly Significant Difference
ICH	=	International Conference on Harmonisation
ID	=	Internal Diameter
IER	=	Ion Exchange Resin
IS	=	Internal Standard
k_e	=	Elimination rate constant
Kg	=	Kilogram
L-HPC	=	Low-substituted Hydroxypropyl Cellulose
LLE	=	Liquid-Liquid Extraction
LOD	=	Limit Of Detection
LOQ	=	Limit Of Quantification
M	=	Molar
mg	=	Milligram
min	=	Minute
mm	=	Millimeter
ml	=	Milliliter
MP Na	=	Methylparaben sodium
nm	=	Nanometer
N	=	Theoretical plates
ng	=	Nanogram

ODT	=	Orally Disintegrating Tablet
PP Na	=	Propylparaben sodium
PPT	=	Protein Precipitation Technique
PVP	=	Polyvinylpyrrolidone
QC	=	Quality Control
RE	=	Relative Error
RH	=	Relative Humidity
RPM	=	Rotation Per Minute
RSD	=	Relative Standard Deviation
SD	=	Standard deviation
Sec	=	Second
SSG	=	Sodium Starch Glycolate
T_{max}	=	Time taken to reach maximum plasma concentration
$t_{½}$	=	Half life
USFDA	=	United States Food and Drug Administration
USP	=	United States Pharmacopoeia
UV	=	Ultraviolet
v/v	=	Volume by Volume
w/v	=	Weight by Volume
µg/ml	=	Microgram per Milliliter
µl	=	Microliter

LIST OF APPENDICES

LIST OF PUBLICATIONS & PRESENTATIONS

1 Ravi Sheshala, Yusrida Darwis, Nurzalina Khan (2009). Development and validation of an RP-LC-UV method for the determination of ondansetron: Application to pharmaceutical dosage forms. *Chromatographia*. **70**, p. 75-81.

2 S. Ravi, Y. Darwis, and N. Khan (2009). Development and validation of an RP-HPLC-UV method for analysis of sumatriptan succinate in pharmaceutical dosage forms. *Acta Chromatographica*. **21**, p. 421-432.

3 Ravi Sheshala, Yusrida Darwis, Nurzalina Abdul Karim Khan (2009). Formulation and Evaluation of Taste Masked Sumatriptan Succinate Orally Disintegrating Tablets. *Malaysian Journal of Pharmacy*, 1, S39.

4 S. Ravi, N. Khan and Y. Darwis. Development and Validation of RP-HPLC-UV Method for the Determination of Ondansetron in Rabbit Plasma: Application to Pharmacokinetic Study. *Acta Chromatographica* (Article in Press).

5 Ravi Sheshala, Yusrida Darwis, Nurzalina Abdul Karim Khan (2007). Development and Validation of RP-HPLC-UV Method for Determination of Sumatriptan Succinate: Application to Pharmaceutical Dosage Forms. *USM-UNAIR first collaborative conference*, 13th-14th June 2007, Penang, Malaysia.

6 Ravi Sheshala, Yusrida Darwis, Nurzalina Abdul Karim Khan (2008). Formulation and Evaluation of Ondansetron Orally Disintegrating Tablets Using Different Superdisintegrants. *Asean Scientific Conference in Pharmaceutical Technology*, 1st-3rd June 2008, Penang, Malaysia.

7 Ravi S, Kanakal, MM, Nurzalina AKK, Yusrida D. (2009) Formulation and Evaluation of Ondansetron Orally Disintegrating Tablets Using Lyophilization Technique. *UNAIR-USM second collaborative conference*, 10th-11th February 2009, Indonesia.

8 Ravi Sheshala, Yusrida Darwis, Nurzalina Abdul Karim Khan (2009). Formulation and Evaluation of Taste Masked Sumatriptan Succinate Orally Disintegrating Tablets Using Orasolv Technique. *Symposium of USM Fellowship Holders*, 14th- 15th November 2009, Penang, Malaysia.

9 Ravi Sheshala, Yusrida Darwis, Nurzalina Abdul Karim Khan (2010). Development And Evaluation Of Taste Masked Orally Disintegrating Tablets Of Water Soluble And Water Insoluble Drugs. Universiti Sains Malaysia, Penang, Malaysia.

PEMBANGUNAN DAN PENILAIAN TABLET TERKECAI ORAL TERLINDUNG RASA UNTUK SATU DRUG LARUT AIR, SUMATRIPTAN SUKSINAT DAN SATU DRUG TIDAK LARUT AIR, ONDANSETRON

ABSTRAK

Tujuan penyelidikan ini dijalankan adalah untuk menformulasikan tablet terkecai oral terlindung rasa (ODTs) ordansetron (tidak larut air) dan sumatriptan suksinat (larut air) menggunakan teknologi-teknologi berlainan yang sedia ada iaitu Orasolv, pengeringan sejuk beku dan Wowtab. Dalam teknik Wowtab dan pengeringan sejuk beku, rasa pahit ordansetron telah dilindungi dengan penambahan suatu pemanis (aspartam), manakala dalam teknik Orasolv melalui pengkompleksan drug dengan Eudragit EPO (1:0.5). Dalam kesemua teknik yang digunakan untuk penyediaan ODTs sumatriptan suksinat, rasa drug yang sangat pahit telah dilindungi melalui penyalutan dengan Eudragit EPO (1:1) menggunakan kaedah pengeringan semburan. Dalam teknik Wowtab, formulasi ordansetron dan sumatriptan suksinat telah disediakan menggunakan jenis dan kepekatan superdisintegran yang berbeza. Teknik Wowtab dan pengeringan sejuk beku menghasilkan formulasi tablet ordansetron yang optimum dengan masa pengecaian in vitro dan kandungan air menepati syarat USP iaitu masing-masing $\leq$ 10 saat dan $\leq$4%. Namun, tiada formulasi ordansetron yang disediakan melalui teknik Orasolv menepati syarat-syarat rasmi untuk masa pengecaian in vitro. Sebaliknya, ketiga-tiga teknik (Orasolv, pengeringan sejuk beku dan Wowtab) telah menghasilkan formulasi sumatriptan suksinat optimum yang memenuhi syarat rasmi USFDA untuk masa pengecaian in vitro selama $\leq$60 saat. Profil pelepasan in vitro untuk formulasi yang optimum bagi kedua-dua drug adalah setanding dengan produk komersial. Formulasi optimum bagi ordansetron dan sumatriptan suksinat yang disediakan menggunakan teknik Wowtab telah dipilih untuk penilaian rasa, perasaan di dalam mulut dan masa pengecaian in vivo

menggunakan sukarelawan-sukarelawan manusia. Formulasi ordansetron dan sumatriptan suksinat yang optimum mempunyai rasa yang sedap, perasaan di dalam mulut yang bagus dan mengecai di dalam mulut dalam masa, masing-masing 12 dan 41 saat. Tambahan pula, kedua-dua formulasi yang optimum adalah stabil untuk sekurang-kurangnya 6 bulan pada 40 °C/75% RH dan 25 °C/65% RH. Formulasi ordansetron yang optimum terdiri daripada poliplasdon XL-10 (15%), aspartam (7%) dan perisa strawberi (1%) manakala sumatriptan suksinat mengandungi Kollidon CL-SF (5%), ammonium bikarbonat (10%), aspartam (2%) dan perisa nanas (0.75%). Dua kaedah HPLC isokratik yang spesifik dan sensitif untuk penentuan ondansetron dan sumatriptan suksinat dalam plasma telah dibangunkan dan divalidasi secara berasingan. Keputusan berselang kerpercayaan 90% bagi C_{max} dan $AUC_{0-\infty}$ yang didapati daripada ujian biokeperolehan menunjukkan bahawa kadar dan tahap penyerapan formulasi Rujukan dan Ujian bagi ondansetron dan sumatriptan suksinat adalah biosetara. Kesimpulannya, ODTs ordansetron dan sumatriptan suksinat terlindung rasa telah disediakan dengan jayanya dan mungkin berguna sebagai alternatif kepada produk-produk komersial yang sedia ada.

DEVELOPMENT AND EVALUATION OF TASTE MASKED ORALLY DISINTEGRATING TABLETS OF A WATER SOLUBLE DRUG, SUMATRIPTAN SUCCINATE AND A WATER INSOLUBLE DRUG, ONDANSETRON

ABSTRACT

The aim of the present research was to formulate taste masked orally disintegrating tablets (ODTs) of ondansetron (water insoluble) and sumatriptan succinate (water soluble) using different available technologies namely Orasolv, freeze drying and Wowtab. In Wowtab and freeze drying techniques, the bitter taste of ondansetron was masked by the addition of a sweetener (aspartame), whereas in the Orasolv technique by complexing the drug with Eudragit EPO (1:0.5). In all the techniques used to prepare sumatriptan succinate ODTs, the intensely bitter taste of the drug was masked by coating it with Eudragit EPO (1:1) using spray dryer. In Wowtab technique, ondansetron and sumatriptan succinate formulations were prepared using different types and concentrations of superdisintegrants. The Wowtab and freeze drying techniques produced optimized formulations of ondansetron tablets with an in vitro disintegration time and water content within the USP requirement of ≤10 sec and ≤4%, respectively. However, none of the ondansetron formulations prepared by Orasolv technique met the official requirements for in vitro disintegration time. On the other hand, the three techniques (Orasolv, freeze drying and Wowtab) produced optimized formulations of sumatriptan succinate that fulfilled the USFDA official requirements for in vitro disintegration time of <60 sec. The in vitro release profiles of the optimized formulations for the two drugs were comparable with the commercial products. The optimized formulations of ondansetron and sumatriptan succinate prepared by Wowtab technique were selected for the evaluation of taste, mouth feel and in vivo disintegration time using human volunteers. The optimized

formulations of ondansetron and sumatriptan succinate had a pleasant taste with good mouth feel and disintegrated in the mouth within 12 and 41 sec, respectively. In addition, both optimized formulations were stable for at least 6 months at 40 °C/75% RH and 25 °C/65% RH. The optimized formulation of ondansetron consisted of Polyplasdone XL-10 (15%), aspartame (7%) and strawberry flavour (1%) whereas sumatriptan succinate consisted of Kollidon CL-SF (5%), ammonium bicarbonate (10%), aspartame (2%) and pineapple flavour (0.75%). Two specific and sensitive isocratic HPLC methods for the determination of ondansetron and sumatriptan in plasma were developed and validated separately. The 90% confidence interval results of C_{max} and $AUC_{0-\infty}$ obtained from the bioavailability studies demonstrated that Reference and Test formulations of ondansetron and sumatriptan succinate are bioequivalent in their rate and extent of absorption. In conclusion, taste masked ondansetron and sumatriptan succinate ODTs were successfully prepared and could be useful alternatives to commercially available products.

CHAPTER 1

INTRODUCTION

1.1 Introduction

The most important route for drug delivery is undoubtedly the oral route which has a wide acceptance and accounts up to 50-60% of total dosage forms. Drugs that are administered orally, solid oral dosage forms in general and tablets in particular, represent the preferred class of product. This is due to the convenience in self administration, compactness, ease of manufacturing, accurate dosage, pain avoidance and most importantly patient compliance afforded by those dosage forms (Bhowmik *et al*., 2009; Bharawaj *et al*., 2010). One important drawback of this dosage form is that some patients who suffer from dysphagia (difficulty in swallowing) cannot take their medication as prescribed by their doctor, resulting in a high incidence of non-compliance and therapy failure. A survey conducted in Norway revealed that 26% out of 6158 patients experienced difficulty in swallowing conventional tablets due to their large size and taste of the tablets (Anderson *et al*., 1995; Frijlink, 2003; Chandrasekhar *et al*., 2009). This difficulty is common among all age groups and more specific with paediatric, geriatric and bedridden or disabled patients and also patients with persistent nausea and vomiting, those who are travelling and those who have little or no access to water (Seager, 1998; Wagh *et al*., 2010). For example, a very elderly patient may not be able to swallow a daily dose of antidepressant due to hand tremors and dysphagia. An eight year-old child with allergies has difficulty in ingesting anti-histamine syrup due to the underdeveloped muscular and nervous system and desires for a more convenient dosage form than syrup. An institutionalised schizophrenic patient can hide a conventional tablet under the tongue to avoid his/her daily dose of an atypical antipsychotic. A middle aged

woman undergoing radiation therapy for breast cancer may be too nauseous to swallow H_2-blocker (Hirani *et al*., 2009; Prajapati and Ratnakar, 2009). A migraine patient who is travelling with little or no access to water may not be able to consume the conventional tablet due to the risk of choking. Hence, development of a patient friendly solid oral dosage form that disintegrate/dissolve rapidly in the mouth when in contact with saliva has attracted substantial attention in both academia and industry in order to address swallowing difficulties associated with the conventional solid oral dosage forms (Sastry *et al*., 2000; AlHusban *et al*., 2010a). This dosage form is commonly referred to as orally disintegrating tablets (ODTs) which are a perfect fit for all the patients aforementioned.

United States Food and Drug Administration (USFDA) defined ODT as "A solid single unit dosage form containing active ingredient which disintegrates rapidly usually within a matter of seconds when placed upon the tongue (USFDA, 2008)." The disintegration time for ODTs generally ranges from several seconds to about a minute (Bandari *et al*., 2008). European Pharmacopoeia adopted the term 'orodispersible tablets' for tablets that disperse/disintegrate rapidly in the mouth before being swallowed and which should disintegrate within 3 min (European Pharmacopoeia, 2002). These tablets are also called as quick disintegrating tablets, mouth dissolving tablets, fast disintegrating tablets, fast dissolving tablets, rapid dissolving tablets, melt-in-mouth tablets, porous tablets and repimelts. All of these terms were approved by United States Pharmacopoeia (USP 30, 2007).

Recent market surveys indicate that more than half of the patient population prefer ODTs to other dosage forms and most consumers would ask their doctors for ODTs

(70%), purchase ODTs (70%), or prefer ODTs to regular tablets or liquids (>80%) (Brown, 2001; Deepak, 2004). These responses may be attributed to the ODT advantages such as ease of administration, ease of swallowing, pleasant taste and the availability in several flavours (Seager, 1998). ODTs also offer clinical advantages such as improved safety (risk of choking or suffocation due to physical obstruction with oral administration of conventional tablets is avoided) and, in some cases, improved efficacy (increased bioavailability of drugs that are absorbed from mouth, pharynx and oesophagus). In addition, several business needs are driving ODT technology development and the commercialization of new products such as the need for expanded product lines, improved life-cycle management, extended patent life, and marketing advantages (Seager, 1998; Brown, 2001). The summary of ODT products available in the market are listed in Table 1.1.

Table 1.1: Summary of commercially available ODT products.

Trade name	Active ingredient	Category	Manufacturer
Abilify Discmelt	Aripiprazole	Antipsychotic	Bristol-Myers Squibb
Alavert	Loratadine	Antihistamine	Wyeth
Aricept ODT	Donepezil HCl	Cholinomimetic	Eisai and Pfizer
Benadryl Fastmelt	Diphenhydramine	Anticholinergic	Pfizer
Benadryl Allergy & Sinus Fastmelt	Diphenhydramine & pseudoephedrine	Anticholinergic and antiallergic	Pfizer
Benadryl Fastmelt	Diphenhydramine & pseudoephedrine	Anticholinergic and antiallergic	Warner Lambert
Children's Dimetapp ND	Loratadine	Antihistamine	Wyeth
Cibalginadue Fast	Ibuprofen	NSAID	Novartis
Claritin RediTabs	Loratadine	Antihistamine	Schering Plough
Clarinex RediTabs	Desloratadine	Antihistamine	Schering Plough
Domray MD	Domperidone	Antiemetic	Ray Remedies
Excedrin Quick Tabs	Acetaminophen	Analgesic and antipyretic	Bristol-Myers Squibb
Fazalco	Clozapine	Antipsychotic	Alamo Pharmaceuticals
Febrectol	Paracetamol	Analgesic and antipyretic	Prographarm
Feldene Melt	Piroxicam	NSAID	Pfizer

Table 1.1: continued……

Fluoxetine ODT	Fluoxetine	Antidepressant	Bioavail
Gaster D	Famotidine	Anti ulcer	Yamanouchi
Hyoscyamine sulfate ODT	Hyoscyamine sulfate	Anticholinergic	ETHEX Corporation
Imodium Instant melts	Loperamide HCl	Antidiarrheal	Janssen
Kemstro	Baclofen	Muscle relaxant	Schwarz Pharma
Klonopin Wafers	Clonazepam	Antiepileptic	Roche
Kid Relief	Acetaminophen	Analgesic and antipyretic	Ethypharm
Maxalt-MLT	Rizatriptan Benzoate	Antimigraine	Merck
Mosid MT	Mosapride	Prokinetic	Torrent
Nimulid MD	Nimesulide	NSAID	Panacea Biotech
Nasea OD	Ramosetoron	Antiemetic	Yamanouchi
NuLev	Hyoscyamine sulfate	Anticholinergic	Schwarz Pharma
Nurofen Flash Tab	Ibuprofen	NSAID	Boots Healthcare
Orapred ODT	Prednisolone	Corticosteroid	Sciele Pharma
Pepcid ODT	Famotidine	Antiulcer	Janssen
Permax	Pergolide	Antiparkinson	Amarin Corporation
Propulsid Quicksolv	Cisapride monohydrate	Prokinetic	Janssen
Ralivia Flashdose	Tramadol HCl	Opioid analgesic	Bioavail
Rapimelt	Zolmitriptan	Antimigraine	Astra Zeneca
Remeron SolTab	Mirtazapine	Antidepressant	Organon Inc
Risperidal M-Tab	Risperidone	Antipsychotic	Janssen
Rofaday MT	Rofecoxib	Antiinflammatory	Lupin
Romilast	Montelukast	Antiasthma	Ranbaxy
Tempra Quicklets	Acetaminophen	Analgesic and antipyretic	Bristol-Myers Squibb
Torrox MT	Rofecoxib	Antiinflammatory	Torrent
Valus	Valdecoxib	Antiinflammatory	Glenmark
Zelepar	Selegiline	Antiparkinson	Elan Corporation
Zofran ODT	Ondansetron	Antiemetic	GlaxoSmithKline
Zolpidem ODM	Zolpidem tartarate	Antipsychotic	Bioavail
Zomig ZMT	Zolmitriptan	Antimigraine	Astra Zeneca
Zotacet MD	Cetrizine HCl	Antiallergic	Zota Pharma
Zubrin	Tepoxaline	Canine NSAID	Schering Corporation
Zyprexa Zydis	Olanzapine	Antipsychotic	Eli Lilly

1.2 Ideal properties of ODTs

Below are the ideal properties of ODTs reported by some authors (Habib *et al*., 2000; Bradoo, 2001; Hirani *et al*., 2009). The ODT should:

- not require water to swallow, but it should dissolve or disintegrate in the mouth within a few seconds
- leave minimal or no residue in the mouth after oral administration
- have a smooth mouth feel and pleasant taste
- be compatible with taste masking procedures and other excipients
- have sufficient strength to withstand the rigours of the manufacturing process and post manufacturing handling
- allow high drug loading
- exhibit low sensitivity to environmental conditions such as humidity and temperature
- be adaptable and amenable to existing processing and packaging machineries
- be cost effective

1.3 Advantages of ODTs

The advantages of ODTs reported by some authors (Kuchekar *et al*., 2003; Shukla *et al*., 2009; Gupta *et al*., 2010; Sahoo *et al*., 2010) are listed below:

- Ease of administration to the patients who cannot swallow, such as the elderly, stroke victims and bedridden patients; patients who should not swallow, such as renal failure patients and patients who refuse to swallow, such as paediatric, geriatric and psychiatric patients.
- Improved compliance and administration convenience for travellers and busy people who do not have instant access to water.

- Pleasant taste and good mouth feel property of ODTs help to change the perception of medication as "bitter pill", particularly in paediatric patients due to improved taste of bitter drugs.
- Convenience of administration and accurate dosing as compared to liquid formulations.
- Ability to provide liquid medication advantages in the form of solid preparation.
- Pregastric absorption of some drugs from mouth, pharynx and oesophagus as the saliva passes down to the stomach can result in improved bioavailability, reduced dose and improved clinical performance by reducing side effects.
- Risk of choking or suffocation during administration of oral conventional tablets due to physical obstruction is avoided, thus providing improved safety.
- Stability of drug is improved as compared to oral dosage forms like suspension, since the drug remains in solid dosage form till it is consumed. Hence, it combines the advantage of solid dosage form in terms of stability and liquid dosage form in terms of bioavailability.

1.4 Disadvantages of ODTs

A few authors (Aurora and Pathak, 2005; Bhowmik *et al*., 2009; Bharawaj *et al*., 2010) reported that the application of ODT technology is limited by the following disadvantages:

- Drugs with relatively larger doses are difficult to formulate into ODTs
- Patients with Sjögren's syndrome or dryness of the mouth due to decreased saliva production may not be good candidates for these tablet formulations.
- The tablets may leave unpleasant taste and/or grittiness in the mouth if not formulated properly.

- Because they dissolve quickly, ODTs cannot provide controlled or sustained drug release, except those that contain slow-dissolving, microparticulate-coated drugs, which quickly disperse and are swallowed.
- Fragile products require special unit-dose packaging, which may add to the cost. However, few technologies like Wowtab, Durasolv and AdvaTab can produce sufficiently hard and durable tablets to be packaged in multi-dose bottles.

1.5 Challenges in the formulation of ODTs

Hirani *et al*. (2009) and Bharawaj *et al*. (2010) described the challenges in the formulation of ODTs. Below are the summary of their report.

1.5.1 Mechanical strength and disintegration time

ODTs are formulated to obtain disintegration time usually within a minute. While doing so, maintaining a good mechanical strength is a prime challenge. Many ODTs are fragile and there is a chance of breakage during packing, transport or at the time of handling by the patients. Tablets prepared with technology like Zydis need special type of packaging. It is known that an increase in the mechanical strength will delay the disintegration time of the tablets. Hence, a good compromise between these two parameters is always essential.

1.5.2 Taste masking

Taste is one of the most important parameter governing patient compliance. At present many pharmaceutical drugs are bitter in taste. A tablet of bitter drug which disintegrate in the mouth will seriously affect patient compliance and acceptance of the dosage form. Hence, effective taste masking of the bitter drugs must be done before oral administration.

1.5.3 Mouth feel

Mouth feel is critical and patients should receive a product that feels pleasant. An ODT should not disintegrate into larger particles; resulting in a gritty feeling in the mouth. An ODT should leave minimal or no residue in the mouth after oral administration. In some cases, addition of certain flavours and cooling agents like menthol can imbibe an improved mouth feel perception, resulting in a product that is perceived as being less gritty, even if the only change is the flavour.

1.5.4 Sensitivity to environmental conditions

The ODTs generally should exhibit low sensitivity to environment conditions such as humidity and temperature as most of the excipients used in an ODT preparation are meant to dissolve in minimum quantity of water.

1.5.5 Cost

The technology used for the preparation of an ODT should be acceptable in terms of cost of the finished product. Method like Zydis that require special technologies and specific packaging increase the cost to a remarkable extent.

1.6 Patented technologies for ODTs

Several pharmaceutical and drug delivery companies have patented and commercialized technologies to develop and market ODT products. A list of some patented technologies that produce commercial ODT products are summarized in Table 1.2. A brief description of some patented technologies is described below.

Table 1.2: List of patented technologies and their commercially available products.

Patented technology	Basis of technology	Patent owner	Active ingredient (Brand names)
Zydis	Lyophilization	R.P.Scherer, Inc.	Loratadine (Claritin Reditab and Dimetapp Quick Dissolve)
Lyoc	Lyophilization	Farmalyoc	Phloroglucinol Hydrate (Spasfon Lyoc) Piroxicam (Proxalyoc®) Loperamide (Loperamide-Lyoc®)
Orasolv	Direct compression	Cima Labs, Inc.	Paracetamol (Tempra Quicklets), Zolmitriptan (Zolmig Repimelt)
Durasolv	Direct compression	Cima Labs, Inc.	Hyoscyamine Sulfate (NuLev), Zolmitriptan (Zolmig ZMT)
Wowtab	Direct compression	Yamanouchi Pharmatech, Inc.	Famotidine (Gaster D)
Flashdose	Cottoncandy process	Fuisz Technology Ltd.	Tramadol HCl (Relivia Flash dose)
Flashtab	Direct compression	Ethypharm	Ibuprofen (Nurofen FlashTab)
AdvaTab	Microcaps and diffuscap CR	Eurand International	AdvaTab cetrizine, AdvaTab paracetamol
Oraquick	Micromask taste masking	KV Pharm. Co., Inc.	Hyoscyamine sulfate ODT

1.6.1 Zydis

Zydis is the technology patented by R.P.Scherer. Zydis, the best known of the fast dissolving/disintegrating tablet preparations, was the first marketed new technology tablet. The procedure involved in the manufacturing of ODT using this technique is shown in Fig. 1.1. This process requires the active ingredient to be dissolved or dispersed in aqueous solution of water soluble structure formers. The resultant mixture is poured into the preformed blister packs of a laminate film. The trays holding the blister packs are passed through liquid nitrogen freezing tunnel to freeze the drug solution or dispersion and are subsequently loaded into a freeze dryer. After freeze-drying, the aluminium foil backing is applied on a blister sealing machine

(Kearney and Scherer, 2003). The Zydis dosage form and blister pack are shown in Fig. 1.2.

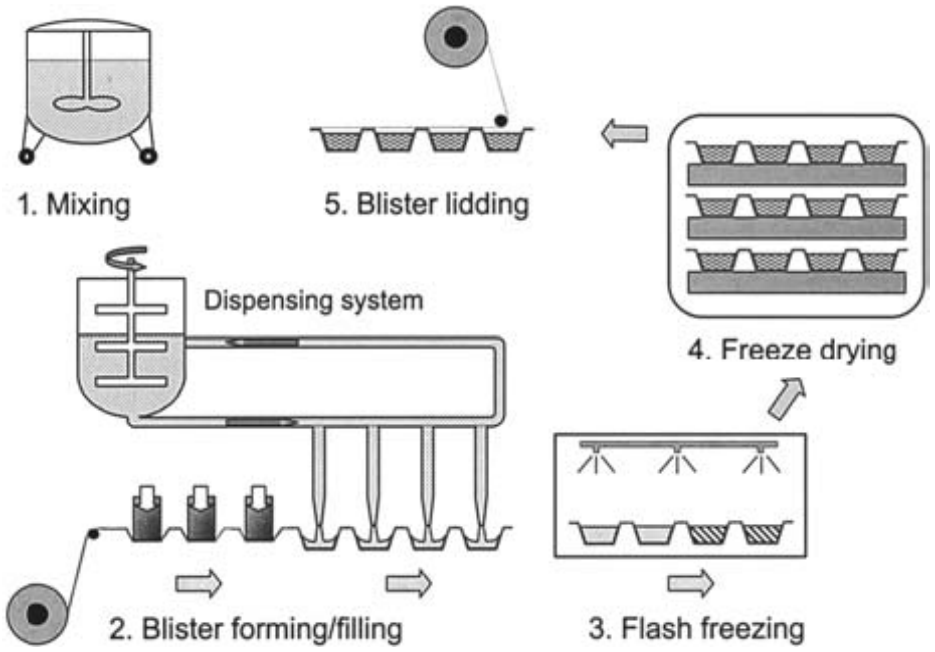

Fig. 1.1: Schematic representation of manufacturing process involved in the Zydis technology (Kearney and Scherer, 2003).

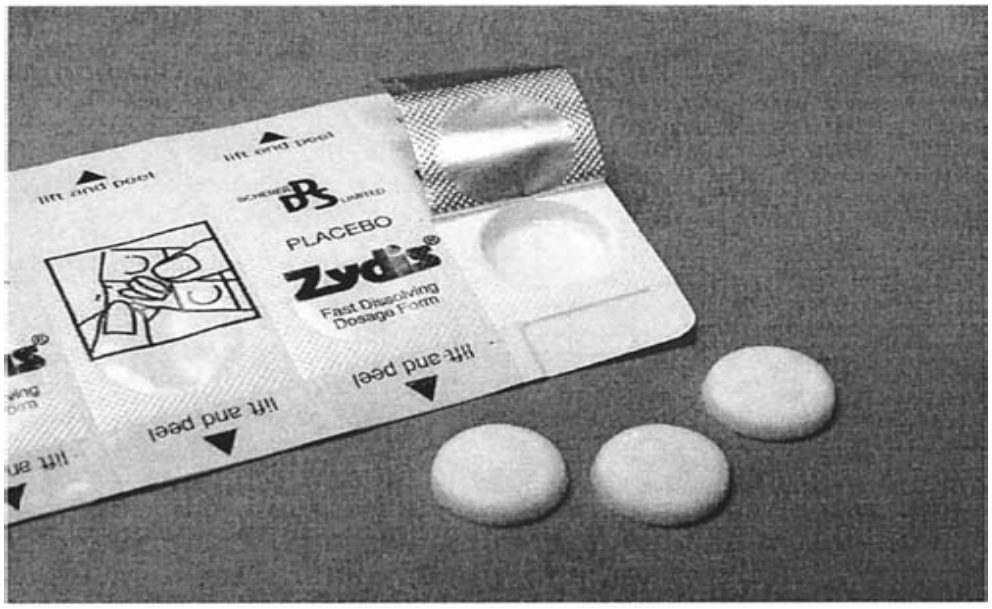

Fig. 1.2: Zydis dosage form and blister pack (Kearney and Scherer, 2003).

Zydis formulation is a unique freeze dried tablet in which drug is physically entrapped or dissolved within the matrix of fast dissolving carrier material. Lyopilization results in preparations which are highly porous with a very high specific surface and disintegrates rapidly. When Zydis units are put into the mouth, the freeze-dried structure dissolves/disintegrates on the tongue in 2 to 3 sec and does not require water to aid swallowing (Kearney and Scherer, 2003; Goel *et al*., 2008). Few of the Zydis products are Claritin Reditab (Loratadine), Maxalt-MLT (Rizatriptan benzoate), Pepcid RPD (Famotidine), Zofran ODT (Ondansetron) and Zyprexa Zydis (Olanzapine). The Zydis matrix is composed of different materials. Polymers or structure formers such as gelatin, dextran or alginates are incorporated in the formulations to impart strength and resilience during handling of the tablets. These form a glossy amorphous structure which imparts strength. To obtain crystallinity, elegance and hardness, saccharides such as mannitol or sorbitol are incorporated. Water is used in the manufacturing process to ensure production of porous units to achieve faster disintegration while various gums are used to prevent sedimentation of dispersed drug particles in the manufacturing process. The Zydis formulation is also self preserving because the final water concentration in the freeze dried product is too low to allow microbial growth. The collapse protectants such as glycine are incorporated to prevent the shrinkage of Zydis units during freeze-drying process or on long-term storage (Bhowmik *et al*., 2009; Ratnaparkhi *et al*., 2009). The Zydis formulation utilizes flavours and sweeteners to optimize the taste of the dosage form. In addition, it also utilizes microencapsulation techniques with specialized polymers or complexation with ion exchange resins to mask the bitter taste of the drug (Prajapati *et al*., 2009). Zydis products are light weight and fragile

and must be packed in blister packs to protect the formulation from moisture in the environment and it may degrade at humidity greater than 65% (Bandari *et al*., 2008).

The major advantage of the Zydis formulation is convenience in administration of the product. Due to dispersion and dissolution in saliva while still in the oral cavity, there can be a substantial amount of pregastric absorption (buccal, pharyngeal and gastric regions) from the Zydis product which can increase bioavailability of some drugs compared to traditional tablets. The main disadvantages of this dosage form are they are relatively expensive and the production process is time consuming, fragility makes conventional packaging unsuitable for these products, difficult for the aged patients to handle because of inadequate strength, poor stability at higher temperatures and humidities and their limited ability to incorporate higher concentrations of active drug (Schiermeier and Schmidt, 2002; Prajapati *et al*., 2009).

1.6.2 Lyoc

Lyoc technology is patented by PHARMALYOC. Lyoc technology lyophilizes an aqueous solution, suspension, or emulsion of drug and excipients. Lyoc's high degree of porosity yields shorter disintegration times (2 to 20 sec) than compressed tablets. Lyoc utilizes a freeze drying process but it differs from Zydis in that the product is frozen on the freeze dryer shelves. The liquid solution or suspension preparation evolves fillers, thickening agents, surfactant, non-volatile flavouring agents and sweeteners along with drug. This homogeneous liquid is prepared and placed directly into blister cavities followed by freeze drying. Non-homogeneity by sedimentation during freeze drying is avoided by incorporating a large proportion of undissolved inert filler (mannitol) to increase the viscosity of the emulsion. However,

the incorporation of high proportion of filler reduces the porosity of the tablets and as a result; the disintegration process becomes slower (Kearney and Scherer, 2003; Bandari *et al*., 2008; CIMA Labs, 2008; Wagh *et al*., 2010).

1.6.3 Orasolv

Orasolv technology is patented by CIMA Labs. The process includes use of effervescent disintegrating agents compressed with low pressure to produce the ODT. These prepared tablets disperse in the saliva in less than one minute with the aid of incorporated effervescent disintegrating agent (Bandari *et al*., 2008). The effervescent disintegrating pairs include an acid source (citric acid and tartaric acid) and a carbonate source (sodium bicarbonate and sodium carbonate); they release carbon dioxide gas as they come in contact with water (Wehling *et al*., 1993; Wagh *et al*., 2010). The unpleasant taste of a drug is not merely counteracted by sweeteners or flavours; both coating the drug powder and effervescence are means of taste masking in Orasolv. Conventional blenders and tablet machines are used to produce the tablets and the tablet has the appearance of a traditional compressed tablet. However, the mixture of drug and excipients are compressed at low pressure in order to decrease the disintegration time which yields a soft and brittle tablet in comparison with conventional tablets (Prajapati *et al*., 2009). For this reason, CIMA developed a special packaging system, Paksolv to protect tablets from breaking during transport and storage. The typical Paksolv package is shown in Fig. 1.3. It is a dome shaped blister package, prevents vertical movement of tablet with the depression and also offers light and moisture resistance (Amborn and Tiger, 2001; Bandari *et al*., 2008). An advantage with the low degree compression force of Orasolv is that the particle coating used for taste masking is not compromised by fracture during processing.

The products formulated with this technique are Tempra FirsTabs (Acetaminophen) and Remeron SolTab (Mirtazapine).

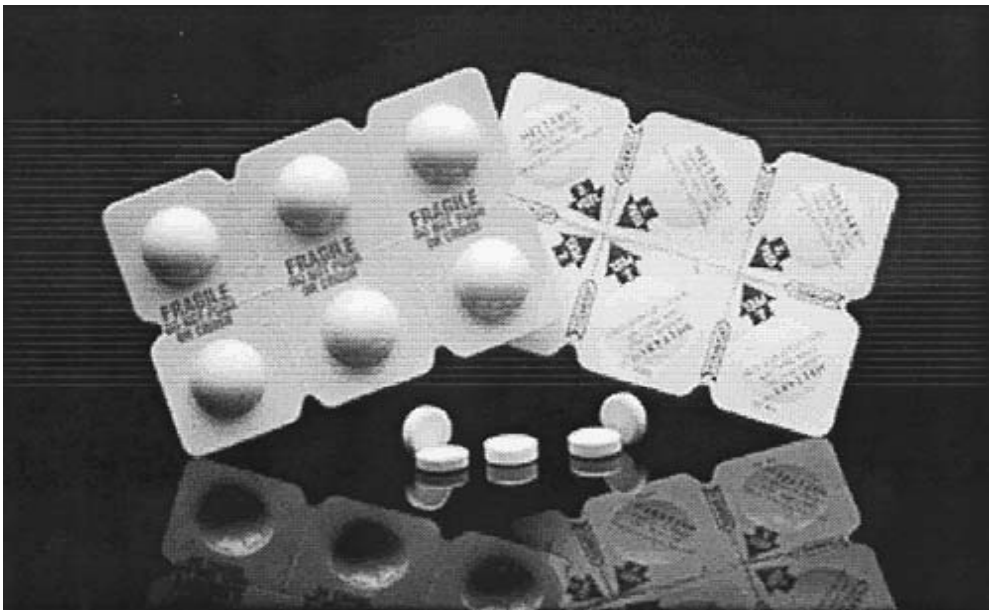

Fig. 1.3: Typical Paksolv package (Pather *et al*., 2002).

1.6.4 Durasolv

Durasolv is the patented technology of CIMA Labs. The tablets produced by this technique are produced in a similar fashion to that of Orasolv but they have much higher mechanical strength due to application of higher compaction pressures during tableting. Tablets formulated by this technology consist of drug, non-direct compression filler (dextrose, mannitol, sorbitol, lactose and sucrose) and lubricant. Tablets are prepared using conventional tabletting equipment and have good rigidity. These tablets are so durable that they can be packed into either conventional packaging system like blisters or vials. Durasolv is an appropriate technology for low dose drugs. The limitations of this technique is its low drug loading capacity and high compaction pressure which are not suitable for incorporation of taste masked coated pellets. The coated pellets may be fractured during compaction, and the bitter-

tasting drug may be exposed to the patient's taste buds. Therefore, this technique is best suited for formulations containing relatively small doses of active ingredient (Khankari *et al*., 2000; Prajapati *et al*., 2009; Ratnaparkhi *et al*., 2009; Sahoo *et al*., 2010; Wagh *et al*., 2010). The currently available products using this technology are NuLev (Hyosciamine sulphate) and Zomig ZMT (Zolmitriptan).

1.6.5 Wowtab

Wowtab technology is patented by Yamanouchi Pharmaceuticals. 'Wow' means "without water". The Wowtab technology utilizes sugar and sugar-like (e.g., mannitol) excipients. This technology employs combination of low and high mouldability saccharides to produce ODT using conventional granulation and tableting methods. The combination of low (lactose, mannitol, glucose, sucrose and xylitol) and high mouldability saccharides (maltose, maltitol and sorbitol) is used to produce a rapidly melting tablet. When the low and high mouldable saccharides are used alone, the desired properties of hardness and quick disintegration cannot be achieved simultaneously, hence combinations are used. The active ingredient is mixed with low mouldability saccharides and granulated with high mouldability saccharides as binder and then compressed into tablet. Due to its significant hardness, the Wowtab formulation is a bit more stable to the environment than the Zydis or Orasolv. It is suitable for both conventional bottle and blister package (Venkateswara *et al*., 2000; Allen *et al*., 1998; Bandari *et al*., 2008; Bhowmik *et al*., 2009; Prajapati *et al*., 2009; Wagh *et al*., 2010). Two Wowtab formulations currently in the US market are Benadyl Allery & Sinus FASTMELT (Diphenhydramine) and Children's Benadyl Allergy & Cold FASTMELT (Diphenhydramine and Psuedoephedrine).

1.6.6 Flashdose

Flashdose technology has been patented by Fuisz and is also known as shearform technology. Flashdose tablets consist of self-binding shearform matrix termed as "floss". Shearform matrices are prepared by flash heat processing. This technology utilizes a unique spinning mechanism to produce a floss-like crystalline structure, much like cotton candy. The floss is a fibrous material commonly made of saccharides such as sucrose, dextrose, lactose and fructose at temperatures ranging between 180-250 °C. This crystalline sugar can then incorporate the active drug and be compressed into a tablet. The final product manufactured by this process is highly porous in nature. Hence, it disperses and dissolves quickly once placed onto the tongue and also offer very pleasant mouthfeel due to fast solubilization of sugars in presence of saliva. The characteristics of the product can be altered greatly by changing the temperature and other conditions during production. Instead of a floss-like material, small spheres of saccharides can be produced to carry the drug. The process of making these microspheres is known as Ceform and it serves as an alternative method for taste masking of bitter drug (Myers *et al.*, 1995; Fuisz, 1997; Agarwal *et al*., 2006; Wagh *et al*., 2010). Nurofen meltlet, a new form of ibuprofen as melt in mouth tablets was prepared using flashdose technology (Manivannan, 2009; Shukla *et al*., 2009).

1.6.7 Flashtab

Flashtab technology is yet another fast dissolving/disintegrating oral tablet formulation. Prographarm laboratories have patented this technology. Tablet prepared by this system consists of an active ingredient in the form of microcrystals. The coacervation, microencapsulation and extrusion spheronisation techniques might

be used to prepare these drug microgranules. This technique utilizes conventional tableting technology and also used similar excipients as in conventional compressed tablets. The two types of excipients used in this technology are disintegrating agents (polyvinylpyrrolidone or carboxymethyl cellulose) and swelling agents (carboxymethyl cellulose, starch and microcrystalline cellulose). A combination of these two excipients is mixed with coated drug particles in this formulation to produce a tablet that disintegrates in the mouth within one minute (Cousin *et al*., 1995; Bandari *et al*., 2008; Bhowmik *et al*., 2009). Nurofen Flashtab (Ibuprofen) was prepared by Ethypharm using this technique.

1.6.8 Frosta

Akina patented this technology. Frosta technology is based on the compression of highly plastic granules at low pressures to produce strong tablets with high porosity. The simplified manufacturing process of Frosta is shown in Fig. 1.4. The process to prepare highly plastic granules involves mixing porous plastic material with water penetration enhancer followed by granulating with binder. The components play an essential role in obtaining tablets with higher strength and faster disintegration due to porosity of the tablet than the other ODTs (Kaushik *et al*., 2004; Fu *et al*., 2005; Jeong *et al*., 2005; Wagh *et al*., 2010).

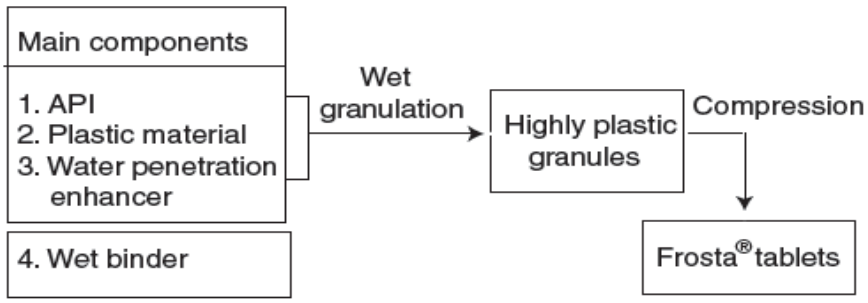

Fig. 1.4: Manufacturing process of Frosta tablets. (API: Active Pharmaceutical Ingredient; Jeong *et al*., 2005).

1.6.9 AdvaTab

Eurand International patented this technology. AdvaTab is distinct from other ODT technologies as it can be combined with Microcaps® taste masking technology and Diffucaps®, controlled release technology. The pairing of AdvaTab with Microcaps® creates products that offer the dual advantage of a patient preferred dosage form, together with a superior taste and smooth mouth feel. This is a critical advantage as the bitter or unpleasant taste of drugs is a significant restriction in the application of other ODT technologies. AdvaTab cetrizine and AdvaTab paracetamol were prepared with this technology (Prajapati *et al*., 2009; Shukla *et al*., 2009; Wagh *et al*., 2010).

1.6.10 Oraquick

This technology is patented by KV Pharmaceuticals. It utilizes a patented taste masking microsphere technology known as MicroMask®. In MicroMask® technology, taste masking process is performed by incorporating drug into matrix microspheres. The tablets are prepared by dissolving the sugar (sucrose, mannitol, sorbitol, xylose, dextrose or mannose) and protein (albumin or gelatin) in a suitable solvent such as water, ethanol, isopropyl alcohol and ethanol-water mixture. The solution of matrix is then spray dried to yield highly porous granules. The formed granules are then mixed with drug and other excipients and compressed at low compression force. The microspheres in the form of matrix protects drug which can be compressed with sufficient mechanical strength without disrupting taste-masking matrix. Lower heat of production than other fast disintegrating technologies makes Oraquick appropriate for heat sensitive drugs. KV Pharmaceuticals has products in

development such as analgesics, drugs for cough and cold, psychotropics and anti-infectives (Bandari *et al*., 2008; Prajapati *et al*., 2009; Wagh *et al*., 2010).

1.7 Manufacturing techniques for ODTs

Many manufacturing techniques have been reported for the formulation of ODTs and a few techniques are discussed below.

1.7.1 Freeze drying or lyophilization

Freeze drying is a process in which water is sublimed from a frozen suspension or solution of drug with structure forming additives. Zydis and Lyoc are patented technologies involving this process to formulate ODTs. This technique allows drying of heat sensitive drugs and biologicals at low temperature under conditions that allow removal of water by sublimation. The drug is entrapped in a water soluble matrix which is freeze dried to produce a tablet with porous open matrix network. The resulting tablet absorbs saliva quickly when placed on the tongue and disintegrates into the lyophilized mass (Bandari *et al*., 2008; Shukla *et al*., 2009; Sahoo *et al*., 2010). Other than active ingredient, the dosage form contains other excipients which increase the quality of final product as discussed in the Section 1.6.1. The researchers, Jaccard and Leyder (1985) used lyophilization technique to prepare an oral formulation that not only dissolved rapidly but also exhibited improved bioavailability for drugs like spironolactone and trolendomycin. Corveleyn and Remon (1997) and Ahmed *et al*. (2006) have formulated freeze dried tablets of hydrochlorthiazide and ketoprofen, respectively using this process.

1.7.2 Moulding

In this technique, moulded tablets are prepared using water soluble ingredients so that the tablets disintegrate readily and dissolve rapidly. Moulding process is of three types i.e. compression moulding, heat moulding and vacuum evaporation without lyophilization (Dobetti, 2001; Wagh *et al*., 2010).

Compression moulding process involves moistening the powder blend with a hydro alcoholic solvent followed by pressing at low pressures in moulded plates to form a wetted mass. The solvent is then removed by air-drying. The tablets manufactured in this manner are less compact than compressed tablets and possess a porous structure that accelerates disintegration/dissolution (Parakh and Gothoskar, 2003; Gupta *et al*., 2010).

The heat moulding process involves preparation of a suspension that contains a drug, agar and sugar (e.g. mannitol). The suspension is poured into the blister packaging wells; the agar solidifies at the room temperature to form a jelly and then drying is carried out at 30 °C under vacuum. In this process, agar solution can be used as a binder and the blister packaging well is used as a mould to manufacture the tablet (Masaki and Ban, 1995; Shukla *et al*., 2009).

The vacuum evaporation without lyophilization process involves pouring of the drug excipient solution/suspension into a mould, freezing the mixture to form a solidified matrix and finally subjecting it to vacuum drying under a temperature within the range of its collapse temperature and equilibrium freezing temperature. This process results in the formation of partially collapsed matrix. This process differs from the

lyophilization technique, as in the former the evaporation of solvent occurs from a solid through the liquid phase to a gas under controlled conditions, instead of the sublimation which takes place in the latter process (Pebley *et al*., 1994).

Tablets produced by moulding process are solid dispersions. Depending on the drug solubility in the carrier, the drug dissolves totally or partially to form a solid solution/dispersion in the carrier matrix. Moulded tablets possess porous structure, which facilitates rapid disintegration and dissolution. These tablets are associated with the problem of poor mechanical strength and they may undergo breakage or erosion during handling and opening of blister packs. However, the mechanical strength of moulded tablets is improved by adding binding agents such as sucrose, acacia or polyvinyl pyrrolidone (Manivannan, 2009; Shukla *et al*., 2009). Patel and Patel (2006) formulated valdecoxib fast dissolving tablets using this technique.

1.7.3 Spray drying

Spray drying technique is widely used in the pharmaceutical industry to produce highly porous and fine powders that dissolve rapidly. The processing solvent is evaporated rapidly by spray drying, which renders the product highly porous and thus can be used in manufacturing ODT. Allen and Wang (1996, 1997 and 2001) and Allen *et al*. (1998) produced a particulate support matrix (spray dried excipient base) for fast dissolving tablets by using a spray drying technique. The components in this matrix include hydrolyzed and non hydrolyzed gelatins, mannitol as a bulking agent, sodium starch glycolate or crosscarmellose or crospovidone as superdisintegrants and ethanol as volatilizing agent (Gupta *et al*., 2010). The surface tension of the droplets is further reduced by incorporating a volatilizing agent and therefore, more pores and

channels are created. To further accelerate disintegration and dissolution, acidic ingredient (citric acid) and/or alkaline ingredients (sodium bicarbonate) might be incorporated. The suspension of above excipients was spray dried to yield a porous powder which was compressed into tablets. The tablets showed rapid disintegration and enhanced dissolution. Tablets manufactured from the spray dried powder have been reported to disintegrate in less than 20 sec in aqueous medium (Bandari *et al*., 2008; Bhowmik *et al*., 2009; Wagh *et al*., 2010). Mishra *et al*. (2006) prepared ODT tablets with Kollidon CL spray dried excipient base and direct compression technique and found that the minimum disintegration time and maximum drug release was observed with the former technique compared to the latter.

1.7.4 Sublimation

The key for rapid disintegration of ODTs is the presence of a porous structure in the tablet matrix. Conventional compressed tablets that contain highly water-soluble ingredients often fail to dissolve rapidly because of low porosity of the matrix. Hence, to generate a porous matrix, volatile ingredients are incorporated in the formulation that is later subjected to a process of sublimation. The steps involved in the sublimation process are depicted in Fig. 1.5. Inert solid ingredients with high volatility like ammonium bicarbonate, ammonium carbonate, benzoic acid, camphor, naphthalene, urea, urethane and phthalic anhydride may be compressed along with other excipients into tablets. This volatile material is then removed by sublimation leaving behind a highly porous matrix. Sublimation of these volatile materials from tablets results in faster disintegration and dissolution as compared with the tablets prepared from granules that were exposed to vacuum. Tablets manufactured by this technique have reported to be disintegrated in 10 to 20 sec. Solvents such as

cyclohexane and benzene were also suggested for generating the porosity in the matrix (Goel *et al*., 2008; Bhowmik *et al*., 2009; Gupta *et al*., 2010; Sahoo *et al*., 2010). Makino *et al.* (1998) reported a method using water as a pore forming agent. Some authors successfully employed sublimation technique in preparation of fast disintegrating tablets (Koizumi *et al.*, 1997; Roser and Blair, 1998; Lee *et al.*, 2002; Patel and Patel, 2008; Kumar *et al*., 2009; Jeevanandham *et al*., 2010).

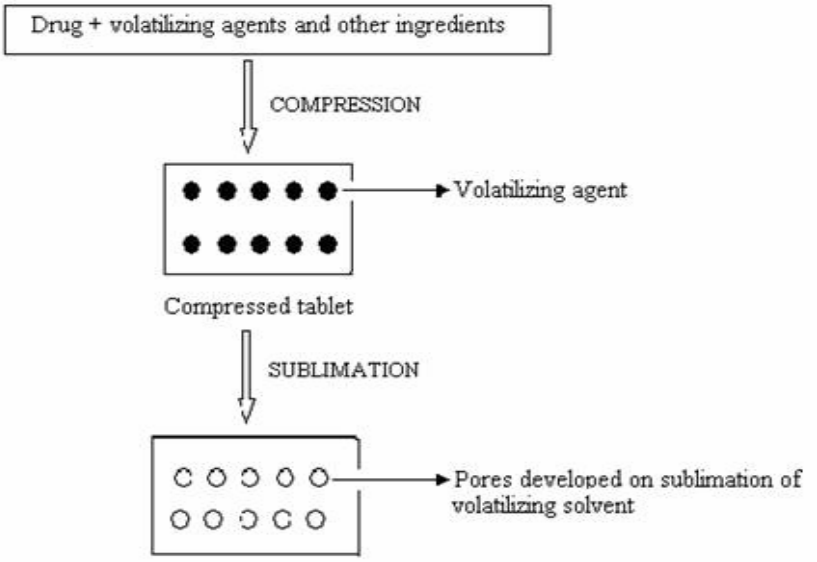

Fig. 1.5: Schematic diagram of sublimation technique for preparation of ODTs. (Ratnaparkhi *et al.*, 2009).

1.7.5 Conventional methods

The most important conventional methods used in formulating ODTs are wet granulation and direct compression techniques.

Wet granulation technique is the most commonly used in tablet manufacture. It is the process of adding a liquid solution and usually a polymeric binder (polyvinyl pyrrolidone or starch) to the powdered starting materials to granulate. In most cases, water is used as a granulating liquid and in certain circumstances where water will

not wet the powder or active substance is unstable in the presence of water, organic solvents such as ethanol or isopropanol alone or in combination are used. This process is performed by mixer granulators and fluidized bed methods (Davies and Discovery, 2004). The process may involve the following steps:

- Deagglomeration of the starting materials by milling or sieving
- Dry mixing of the starting materials
- Liquid addition and wet massing
- Wet sieving to remove large lumps
- Drying and sieving of the dried granules to achieve the desired size distribution.

Different ODT formulations using wet granulation technique were reported by some authors (Gohel *et al*., 2004; Malke *et al*., 2007; Suresh *et al*., 2007; Mohapatra *et al*., 2008; Jeevanandham *et al*., 2010).

Direct compression represents the simplest and most cost effective tablet manufacturing technique. Direct compression is a process where the powder blend of the active ingredient and excipients are compressed on a tablet machine. There is no mechanical treatment of the powder apart from a mixing process. The mixture which is to be compressed must have good flow properties. Low manufacturing cost, usage of conventional equipments, commonly available excipients and a limited number of processing steps justify this as a first method of choice (Davies and Discovery, 2004; Ratnaparkhi *et al*., 2009). At present, this technique is widely applied in the preparation of ODTs because of the availability of improved excipients especially superdisintegrants and sugar based excipients. The detailed description of superdisintegrants and sugar based excipients are discussed in Section 1.9.

Several researchers formulated different ODT formulations using direct compression technique (Schiermeier and Schimdt, 2002; Mahajan *et al*., 2004; Patel and Patel, 2006; Battu *et al*., 2007; Setty *et al*., 2008; Godge *et al*., 2009; Rangaswamy *et al*., 2009; Keny *et al*., 2010).

1.7.6 Mass extrusion

This technology involves softening the active blend using the solvent mixture of water-soluble polyethylene glycol and methanol and subsequent expulsion of softened mass through the extruder or syringe to get a cylindrical shaped extrude which are finally cut into even segments using heated blade to form tablets. This process can also be used to coat granules of bitter drugs to mask their taste (Bhaskaran and Narmada, 2002; Shukla *et al*., 2009). Shishu *et al*. (2007) masked the intensely bitter taste of chlorpheniramine maleate by extrusion method.

1.7.7 Nanonization

This technique was invented by Elan Corporation. Nanomelt technology which involves the reduction of the active ingredient particle size to nano-size (<2000 nm) by various approaches such as wet milling, homogenisation, precipitation and supercritical fluid techniques has been reported. By reducing particle size, the specific surface area of the drug is increased. The nanoparticles are then stabilised against agglomeration by surface adsorption on selected stabilizers to maintain their reduced particle size. Then these nanoparticles are incorporated into ODTs. The result is a stable drug formulation that exhibits an increased dissolution rate. This technique is particularly advantageous for poorly water soluble drugs. Other advantages include fast disintegration/dissolution of nanoparticles leading to