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Current Advances in Drug Delivery Through Fast Dissolving/Disintegrating Dosage Forms

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Vikas Anand Saharan

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Edited by:

Vikas Anand Saharan

Department of Pharmaceutics, School of Pharmaceutical Sciences, Sardar Bhagwan Singh Post Graduate Institute of Biomedical Sciences & Research, Dehradun, India

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FOREWORD

The major challenge that I have experienced as a pharmaceutical science professional is to keep abreast of the ever-evolving developments in the field and translating the innovations to ensure better quality of life to human and animals. The history of pharmaceuticals is loaded with a concern for the development of new chemical entities. Only in recent years, the importance of dosage form design has been recognized as a vital component of safe and effective clinical outcomes.

Despite tremendous innovations in drug delivery, the oral drug delivery continues to be a step ahead as a preferred route of administration for therapeutic agents. Some obvious advantages include accurate dosage, low cost, self-medication, non-invasive and easy administration. At the same time, an important drawback with oral dosage forms is "dysphagia" or difficulty in swallowing in paediatric and geriatric populations, leading to noncompliance and ineffective therapy.

Recent advances in novel delivery systems aim to enhance the safety of drug molecules while maintaining the therapeutic efficacy with an overall aim of better patient compliance. To achieve this objective, the concept of Fast Dissolving/Disintegrating Dosage Forms (FDDF) was introduced. FDDF is a perfect example of patient-oriented pharmaceutical approach, which has emerged from the need to provide a convenient way to administer medicines. Solid dosage forms that disintegrate, dissolve, or get suspended in the saliva in the mouth rapidly (in seconds) without chewing or use of water, provide an excellent alternative to swallowing the solid dosage form. This technique facilitates easy swallowing providing significant benefits to the relevant patient population.

In addition to patient compliance, extending the pharmaceutical product life cycle is another reason for the increasing popularity of the FDDFs. As a drug entity reaches the end of its patent life, it is common for manufacturers to develop it in a new and improved dosage form that allows extension of market exclusivity, while offering its patient population a more convenient dosage form. It also leads to increased revenue for the company, while targeting underserved and undertreated patient populations. Generally, the additional cost of manufacturing these specialized dosage forms is only marginally higher, which is easily compensated by additional benefits to patients.

The book covers relevant topics in different chapters, *e.g.* basic introduction with advantages and key concepts, patented technologies, taste masking approaches, general ingredients for developing formulation, quality control parameters, and critical review of clinical trials, which will be useful for a wide range of readers. The book has also included application of FDDFs to achieve controlled and targeted release which is expected to be of considerable interest to experts as well as new researchers. I strongly feel that this addition to literature will be especially useful to undergraduate pharmacy and post-graduate pharmaceutical science students. The book will serve as a sound source of systematic information for FDDFs. Students and researchers who consider dysphagia or pharmaceutical marketing during innovative product development will find it as a welcoming tool. A single textbook that

brings together inputs from experts in all of these subjects is certainly an invaluable asset to pharmaceutical industry.

I wish to congratulate the editor, team of authors and Bentham publisher for excellent work and contribution to the pharmaceutical sciences. It is especially pleasing to note that a small Master's project undertaken by Dr Vikas Anand in his early years motivated him to continue working in the field and led to this wonderful compilation.

Sanjay Garg
School of Pharmacy and Medical Sciences
University of South Australia, City East Campus
Adelaide, SA
Australia

PREFACE

The solid dosage forms that dissolve or disintegrate quickly in the oral cavity, resulting in solution or suspension, eliminating the need of water for swallowing, are known as fast dissolving/disintegrating dosage forms (FDDFs). Over the last 20 years, the field of FDDFs has expanded considerably to address not only concerns of immediate release dosage forms but additionally played an important role in controlled/modified release drug delivery. This is still an exciting and growing area of pharmaceutical research and education. Ironically, to date no single book provides detailed and specific information on FDDFs. Therefore, I decided to write a book comprising of chapters that collectively address this void and provide an insight into the various technologies and methodologies currently adopted to formulate, prepare and evaluate FDDFs. The idea for this book on the topic has been in mind since my first research project during M.S.(Pharm.) at NIPER, Mohali. Since, then it gradually strengthened when I was Assistant Professor at Seth GL Bihani SD College, Sri Ganganagar and Professor/Associate Professor at Sardar Bhagwan Singh Post Graduate Institute (SBSPGI) of Biomedical Sciences & Research, Dehradun. My teaching and research in relevant and related fields continuously helped me in understanding and developing deeper interests towards FDDFs.

The present book is an attempt to provide comprehensive information to the readers interested in FDDFs. The specific emphasis in this book has been given to various technologies of making FDDFs, formulation development, evaluation, clinical studies, and marketed FDDFs products. This book intends to serve as a source of reference work and some chapters may be used for classroom teaching in graduate/postgraduate programmes. The authors do feel that graduate/postgraduate programmes in pharmaceutical sciences often neglect to adequately address FDDFs as novel drug delivery systems. Research fellows and experience scientists also feel paucity to find few resources outside the primary literature for FDDFs.

Due to its organization into different chapters, the book can be read at different levels and a reader can start as per the sequence of chapters or may opt to go directly onto the desired chapter. Thus, this book could be useful for graduate, postgraduate and PhD students belonging to the pharmaceutical sciences. Nevertheless, we do hope that this book is also useful to expert as well as new researchers, who may find information and new ideas for novel advancements in the field of FDDFs.

I hope that all those who consult this book find it useful as an easy-to-understand text for FDDFs. Constructive comments/suggestions are also invited from readers for further refinements in this book.

CONFLICT OF INTEREST

The authors confirm that they have no conflict of interest to declare for this publication.

ACKNOWLEDGEMENTS

I am grateful and highly indebted to my M.S.(Pharm.) supervisor and teacher Prof.(Dr.) Sanjay Garg for teaching the concepts of research in pharmaceutics and extending his support to this book by writing a foreword to this book. I greatly acknowledge continuous motivation and support of my Ph.D. supervisor Prof.(Dr.) P.K. Choudhury for all my efforts to do the best in the field of pharmaceutical sciences.

I am extremely grateful to the management of SBSPGI, especially Sh. S. P. Singh (Chairman, SBSPGI) and Dr. Gauravdeep Singh (Managing Secretary, SBSPGI) for all round support during my entire tenure at SBSPGI. I am highly privileged to have some of my good teachers, like Dr. Luvkush (academic advisor, SBSPGI), Prof. Veerma Ram and Ms. Urmi Chaurasia, as a constant and continuous source of inspiration and motivation.

Without the support of my mother, father and wife, it was really impossible to complete this arduous task. They have sacrificed a lot of my personal time while I was working on this book. I also missed my son, Inesh, when I was working on this book and he was not beside me.

I would like to thank all the chapter authors for their hard work, valuable contributions and their patience in various phases of publication of this book. I am extremely thankful to Bentham for providing a platform from where this book can reach to it's readers.

Vikas A. Saharan
Department of Pharmaceutics
School of Pharmaceutical Sciences
Sardar Bhagwan Singh Post Graduate Institute
of Biomedical Sciences & Research (SBSPGI)
Balawala, Dehradun
India

List of Contributors

Anupama Singh	Department of Pharmacognosy, School of Pharmaceutical Sciences, Sardar Bhagwan Singh Post Graduate Institute of Biomedical Sciences & Research (SBSPGI), Balawala, Dehradun 248161, India
Arpita Jindal	Department of Clinical Pharmacy, Division of Pharmaceutical Sciences, Shri Guru Ram Rai Institute of Technology and Science, Dehradun 248001, Uttarakhand, India
D. N. Mishra	Department of Pharmaceutical Sciences, Guru Jambheshwar University of Science and Technology, Hisar 125001, Haryana, India
Hemant Jadhav	Department of Pharmacy, Birla Institute of Technology and Science, Pilani Campus, Vidya Vihar, Pilani 333031, Jhunjhunu, Rajasthan, India
Kalpana Nagpal	Amity Institute of Pharmacy, Amity University, Noida, Uttar Pradesh 201303, India
Mahaveer Singh	Department of Pharmacy, Birla Institute of Technology and Science, Pilani Campus, Vidya Vihar, Pilani 333031, Jhunjhunu, Rajasthan, India
Prashant Mathur	Department of Clinical Pharmacy, Division of Pharmaceutical Sciences, Shri Guru Ram Rai Institute of Technology and Science, Dehradun 248001, Uttarakhand, India
Shailendra K. Singh	Department of Pharmaceutical Sciences, Guru Jambheshwar University of Science and Technology, Hisar 125001, Haryana, India
Sokindra Kumar	RV Northland Institute of Pharmacy, Greater Noida 203207, Uttar Pradesh, India
Vandana Kharb	Sachdeva College of Pharmacy, Chandigarh-Ludhiana National Highway, Gharuan 140413, Punjab, India
Vikas A. Saharan	Department of Pharmaceutics, School of Pharmaceutical Sciences, Sardar Bhagwan Singh Post Graduate Institute of Biomedical Sciences & Research (SBSPGI), Balawala, Dehradun 248161, India

DEDICATION

Dedicated to
my Mother Mrs. Chanderpati

&

my Father Mr. Dayanand Saharan

CHAPTER 1

Fast Dissolving/Disintegrating Dosage Forms: Introducing through Development, Market, Pharmacopoeial and Regulatory Status

Vikas A. Saharan[1,*], **Anupama Singh**[2] and **Vandana Kharb**[3]

[1] *Department of Pharmaceutics, School of Pharmaceutical Sciences, Sardar Bhagwan Singh Post Graduate Institute of Biomedical Sciences and Research, Balawala, Dehradun 248161, Uttarakhand, India*

[2] *Department of Pharmacognosy, School of Pharmaceutical Sciences, Sardar Bhagwan Singh Post Graduate Institute of Biomedical Sciences and Research, Balawala, Dehradun 248161, Uttarakhand, India*

[3] *Sachdeva College of Pharmacy, Chandigarh-Ludhiana National Highway, Gharuan 140413, Punjab, India*

Abstract: Fast Dissolving/Disintegrating Dosage Forms (FDDFs) have emerged as alternate dosage forms for patients who cannot swallow or who should not swallow or who refuse to swallow conventional tablets/capsules and liquid formulations. FDDFs include Fast Dissolving/Disintegrating Tablets (FDTs), Fast Dissolving/Disintegrating Oral Films (FDOFs), Fast Dissolving/Disintegrating Capsules (FDCs), Fast Dissolving/Disintegrating Pellets (FDPs), *etc*. These dosage forms dissolve/disintegrate quickly, when placed on tongue, resulting in solution/suspension, which can be swallowed easily and hence do not require water for their oral ingestion. This chapter introduces FDDFs rationale, their brief history, regulatory/pharmacopoeial aspects, advantages/disadvantages and their market potential.

Keywords: Absorption, Capsule, Dysphagia, FDT, Film, Freeze drying, Geriatric, Granule, Mini tablet, Nausea, ODT, Orodispersible, Paediatric, Parkinsonism, Pellet, Pharmacopoeia, Psychotic, Quality of life, Tablet, Travellers.

1. INTRODUCTION

Administering drug by oral route is simple, convenient and a first choice delivery

[*] **Corresponding author Vikas A. Saharan:** Department of Pharmaceutics, School of Pharmaceutical Sciences, Sardar Bhagwan Singh Post Graduate Institute of Biomedical Sciences and Research (www.sbspgi.edu.in), Balawala, Dehradun 248161, Uttarakhand, India; Tel: +91-135-2686246; Mobile: +91-8439820796; Fax: +91-135-2686286; E-mail: vikas.pharmaceutics@gmail.com

option among all other routes of delivering drug. Further, in orally administered dosage forms, the solid dosage forms, *i.e.* tablets and capsules, are mostly liked because of their ease of manufacture, low cost of production, and convenience in packaging and transportation. Conventionally, tablets can be manufactured by either direct compression or granulation methods. Although the basic mechanical compaction approaches for tablet manufacturing remains same. The tablet formulation technology has undergone great improvement and continuous efforts are still ongoing to improve the processes and techniques of tablet manufacturing and physical properties of the tablet *vis a vis* to the latest developments in science.

Sublingual tablets and buccal tablets are considered as precursors to FDDFs. Sublingual tablets have been developed for antianginal drugs like nitroglycerine, *etc.*, where sublingual and/or buccal absorption can provide faster onset of action in acute attacks and improve bioavailability. Buccal tablets are designed to dissolve on the buccal mucous membrane to improve bioavailability of drugs, which are inconvenient to administer parenterally, like steroids and narcotic analgesics. Absorption through buccal route bypasses the gastrointestinal tract for rapid systemic distribution. Not all FDDFs administered orally can offer buccal absorption and bioavailability/faster onset advantages. Most of the FDDFs have similar absorption, bioavailability, onset and similar pharmacokinetics to conventional solid unit dosage forms. However, a fast disintegration of dosage form, rapid dissolution of the drug in oral cavity, and a small tablet weight can enhance absorption in the oral cavity.

US Food and Drug Administration (FDA), in its guidance document *"Size, Shape, and Other Physical Attributes of Generic Tablets and Capsules"*, has emphasised on ability of disintegration to influence oesophageal transit time and the performance of the drug product for its intended use, especially in patients suffering from dysphagia [1]. In one estimate, it was reported that over 16 million people in the US are suffering from some sort of swallowing problems (dysphagia). Dysphagia is "subjective awareness of swallowing difficulty during the passage of a bolus from the mouth to the stomach or the perception of obstruction during swallowing" [2]. Depending on the location of this sensation, dysphagia is classified as oropharyngeal or substernal. Dysphagia may arise due to benign or malignant structural lesions, oesophageal motility abnormalities, oropharyngeal dysfunction (including aspiration), neuromuscular disorders, postsurgical changes and gastro-oesophageal reflux disease (GERD). Dysphagia is also a common consequence of many diseases like pneumonia, dehydration, and malnutrition [3]. Neurological disorders (*e.g.* Parkinson's disease, brain or spinal cord injury, muscular dystrophy, stroke multiple sclerosis) and gastro-

intestinal disorders (GERD, oesophagitis, cancer in oesophagus) are some of the major health problems, which may lead to dysphagia [4]. However, the problem of difficulties in swallowing tablets/capsules is more widespread to 40% of the patient population in US [1]. Paediatric, geriatric and neurologic patients often suffer more from the difficulty of swallowing tablets and capsules [5 - 7]. Tablet swallowing problems have also been observed in adults [3].

In one latest survey, frequent dysphagia was observed in 3% of the US population, uniformly across both gender and all adult ages, and GERD has been indicated as its main underlying cause [8].

FDDFs require less effort to swallow and do not results in increased levels of airway compromise, when swallowing of Orally Disintegrating Tablets (ODTs) is compared to conventional tablets in dysphagic patients [3]. FDDFs are, therefore, considered as an alternate drug delivery option for patients who are either suffering from some sort of dysphagia or patients where compliance is an issue related to size/shape of tablets/capsules or their swallowing ability. FDDFs are comparatively easier dosage form to administer in paediatrics, geriatrics, psychotic, and adult patients who experience dysphagia more often. FDDFs can be administered without water, which makes them more attractive for frequent travellers and situations where access to potable water is an issue. FDDFs improve quality of life in patients by alleviating problems of swallowing, compliance, medication administration without water (nocturea, frequent travellers, nausea) and improving quicker onset of action of medications for immediate action for pain, anxiety, cough-cold, sexual pleasure, anxiety, *etc.* [9 - 14].

2. PHARMACOPOEIAL AND REGULATORY STATUS

FDDFs were first introduced in late 1990s in the market. In the official pharmacopoeial point of view, these formulations are known as orodispersible tablets in European Pharmacopoeia [15] and Orally Disintegrating Tablets in USP [16] and Japanese Pharmacopoeia (JP 16) [17] uses both of these terms. USP, BP and JP have also included several monographs of ODT tablets (Table **1**).

Table 1. Monographs of ODTs in USP 35 NF 30 [16], BP 2010 [19] and JP 16 [17].

USP 35 NF 30	BP 2010	JP 16
Alprazolam Orally Disintegrating Tablet	Orodispersible Mirtazapine Tablets	Ebastine Orally Disintegrating Tablet [17]

CHAPTER 2

Freeze Drying Technologies for Developing Fast Dissolving/Disintegrating Tablets

Vikas A. Saharan*

Department of Pharmaceutics, School of Pharmaceutical Sciences, Sardar Bhagwan Singh Post Graduate Institute of Biomedical Sciences and Research, Balawala, Dehradun 248161, Uttarakhand, India

Abstract: Highly porous nature of freeze dried materials and their ability to retain shape and volume have motivated pharmaceutical scientists to explore application of freeze drying in manufacturing fast dissolving/disintegrating tablets (FDTs). The process of manufacturing lyophilised tablets as FDTs is extensively proprietary and patented. Zydis®, Lyoc®, QuickSolv® and NanoCrystal® Nanomelt™ technologies have been successful in developing drug products and obtaining regulatory clearances from drug regulatory agencies for their marketing authorisations. This chapter aims to discuss formulation, processing and manufacturing aspects of FDTs prepared by freeze drying and also provides an overview on some of these patented FDT technologies.

Keywords: Disintegration, Dissolution, Formulation, Freeze casting, Freeze drying, Gels, Granules, Lyoc®, Lyophilisation, Manufacturing, Matrix, NanoCrystal®, Nanomelt™, Nanoparticles, Patent, Proprietary, QuickSolv®, Tablet, Wafer, Zydis®.

1. INTRODUCTION

Freeze drying is widely used in fabricating amorphous, porous and compact structures that dissolve rapidly. Active ingredient can be entrapped in this water soluble compact structure to prepare a unit dosage form, which can dissolve/disintegrate quickly, either *in vitro* when placed in water or *in vivo* when placed in the oral cavity. The freeze dried matrix of such tablets comprises a water soluble mixture of saccharides and polymers, the proportions of which are optimised to rapid dispersion characteristics and sufficient mechanical strength

* **Corresponding author Vikas A. Saharan:** Department of Pharmaceutics, School of Pharmaceutical Sciences, Sardar Bhagwan Singh Post Graduate Institute of Biomedical Sciences and Research (www.sbspgi.edu.in), Balawala, Dehradun 248161, Uttarakhand, India; Tel: +91-135-2686246; Mobile: +91-8439820796; Fax: +91-135-2686286; E-mail: vikas.pharmaceutics@gmail.com

to withstand handling and transportation stresses. The tablet formulations essentially contain excipients like suspending agents or emulsifiers, viscosity modifiers, wetting agents, preservatives, antioxidants, colours, taste masking agents and flavours, which can either enhance the processing capabilities or improve the quality of the resulting tablets.

2. FREEZE DRYING

Freeze drying or lyophilisation may be defined as the process of removing water from solutions/suspensions/emulsions by sublimation under the influence of high vacuum at temperatures below freezing point of water. The resulting final product is dry and extremely porous. Lyophilisation, as a drying process, was developed in 1940s and till then it has advanced as an important manufacturing step in improving stability of pharmaceutical and biological products [1]. The process is helpful in inhibiting chemical, microbiological and physical degradation pathways that has been otherwise evidenced with the presence of water or residual moisture. Drying at a low temperature has made lyophilisation a safe and extensively applied process for thermolabile actives, pharmaceutical ingredients and biological drugs. Since its inception, lyophilisation has been widely applied in formulating long term stable vaccines, preservation of nucleic acid based pharmaceuticals, preserving red blood cells, and development of micro and nanoparticulate delivery of small molecules, proteins and peptides [2]. Novel lyophilisates have found their applications as FDTs, 3D scaffolds, respirable powders after milling, respirable powders from direct dispersion of lyophilisates and respirable powders from spray-freeze drying.

The freeze drying process essentially involves three steps: an initial freezing of the formulation followed by primary drying and subsequently secondary drying to remove residual moisture from the final product [3]. Liquid drug formulation, solution/suspension/emulsion, filled in vials/tubes/blisters is placed on temperature controlled shelves within a sterile chamber and cooled to low temperatures until solvent freezes. One of the most important targets in freezing step is to achieve uniform freezing of the entire batch. Apart from conventional shelf freezing protocols, other approaches like flash freezing with nitrogen [4, 5] and freezing with annealing [5, 6] are also used for freezing the liquid formulations and optimising the formulation characteristics. Annealing is the process of heating an amorphous substance at a temperature lower than T_g (glass transition temperature) for such a duration that can asymptotically transform it to equilibrium glassy state, resulting in changes in some physical properties like volume, entropy and enthalpy [2]. Primary drying involves reduction of chamber

pressure and raising temperature to sublime the frozen solvent. This drying step may extend from several hours to few days to complete. Primary drying time can be reduced up to 10-30% with controlled nucleation of ice crystals during the initial freezing step [3]. Even after primary drying, some solvent still remains as chemically bound to the solid product, which is finally removed by a desorption process referred to as secondary drying. The drying process is concluded under sub-ambient pressure. Sometimes, primary and secondary drying are coupled in a freeze drier with gradual increase in the temperature for a longer duration (*e.g.* for overnight) [7]. The final dry product retains the shape and volume (fill level) of the container (vial, tube or blister) leading to the formation of a highly porous product.

Freeze drying is a reversible process and addition of water to a freeze dried product readily reconstitutes to its original liquid form, if desired. Freeze drying is frequently used to produce amorphous materials. The use of very low temperatures in the process limits molecular mobility and thereby prevent nucleation of the drug and the excipients resulting in reduction of crystallinity in the final formulation [8]. Optimising the conditions of the freeze drying process may offer a control on the solid state properties of the dried product.

2.1. Lyophilised FDTs: Formulation, Packaging, Advantages and Challenges

FDTs prepared by lyophilisation are highly porous tablets capable of quick oral disintegration/dissolution in the saliva eliminating the need of water for swallowing. However, highly porous tablets may fail due to low hardness and high friability issues, which require a careful optimisation of mechanical strength and quick disintegration time.

The desired attributes of a drug to be incorporated in a lyophilised FDT formulation are low dose, poor water solubility, sufficient chemical stability, fine particle size and tasteless [9, 10]. Ideally, the drug should be poorly water soluble, dose shall be less and a fine particle size range is required to allow formation of a stable aqueous suspension with the matrix components. Problems may arise with soluble drugs due to the formation of eutectic mixtures lowering the freezing point of the formulation, resulting in incomplete freezing or melting during drying. Materials having large particle size may lead to sedimentation problems. High dose actives can be accommodated but with higher dose it becomes difficult to achieve a rapidly dispersing unit. Sufficient aqueous stability is also required to prevent undue degradation of the drug during suspension formation. Very few drugs meet all the essential criteria of an ideal compound. However, certain problems can be resolved by incorporating suspending agents or by adding a

CHAPTER 3

Modifications in Conventional Tablet Compaction Technologies for Developing Fast Dissolving/ Disintegrating Tablets

Vikas A. Saharan*

Department of Pharmaceutics, School of Pharmaceutical Sciences, Sardar Bhagwan Singh Post Graduate Institute of Biomedical Sciences and Research, Balawala, Dehradun 248161, Uttarakhand, India

Abstract: Fast dissolving/disintegrating tablets (FDTs) can be manufactured by direct compression provided the challenge of fast disintegration with adequate mechanical strengths can be addressed. Superdisintegrants, directly compressible coprocessed excipients and water soluble excipients have opened up the flood gates of opportunities in designing and developing FDTs by direct compression. Unacceptable properties of active pharmaceutical ingredient (API), like poor solubility, bitter taste, low bioavailability, may be addressed by making granules, micro-particulates and/or using various coating methods. Such treated API can be used in preparing FDTs. Effervescent agents have also gained attention as disintegrating agents in tablets so as to fasten tablet disintegration time to achieve pharmacopoeial or regulatory compliance for disintegration time. This chapter describes various FDT technologies based on modifications of conventional tablet manufacturing methods. These techniques can be grouped into four categories, *viz.* direction compression, granulation methods, effervescent tablets and direct compression with subsequent treatments.

Keywords: Advatab™, Crystalline transition, Direct compression, DuraSolv®, Easy-tec™, Effervescence, Flashtab®, Frosta®, Granulation, Humidity treatment, OraQuick®, OraSolv®, Pharmaburst®, Phase transition, Ractab®, Sintering, Spray drying, Sublimation, Wowtab®, Ziplet®.

1. INTRODUCTION

The rapid disintegration of FDTs is a result of fast uptake of water within highly

* **Corresponding author Vikas A. Saharan:** Department of Pharmaceutics, School of Pharmaceutical Sciences, Sardar Bhagwan Singh Post Graduate Institute of Biomedical Sciences and Research (www.sbspgi.edu.in), Balawala, Dehradun 248161, Uttarakhand, India; Tel: +91-135-2686246; Mobile: +91-8439820796; Fax: +91-135-2686246; E-mail: vikas.pharmaceutics@gmail.com

porous matrix of FDTs. Manufacturing of FDTs has to face several challenges like mechanical strength, optimum disintegration time, good mouth feel, taste masking, *etc*. Most of the innovations in manufacturing of FDTs are based on two conceptually exclusive characteristics of FDTs. Firstly, disintegration/dissolution time for tablet should be less than one minute and secondly, there should be enough mechanical strength to handle the formulation. The tablet matrix is made highly porous by the addition of disintegrating agents and/or highly water-soluble excipients or by sublimation of water or other subliming materials in the tablet formulation. The use of conventional tablet manufacturing and packaging machinery and ease in technology transfer make them more attractive. Various methods of preparing FDTs by modifications in conventional tablet technologies are shown in Box **1**.

Box 1: Various methods, adapted from conventional tablet compaction methods, for preparing FDTs.

A. **Direct compression**
   Superdisintegrant addition
   Water soluble saccharides/excipients
   Coprocessed excipients
B. **Granulation methods**
   Wet granulation
   Dry granulation
   Melt granulation
   Spray drying
C. **Compaction and subsequent treatments**
   Sublimation
   Humidity treatment followed by drying
   Sintering
D. **Effervescent tablets**

2. DIRECT COMPRESSION

Direct compression is a straightforward, popular and extensively used approach of manufacturing FDTs. Active Pharmaceutical Ingredient (API) is added to directly compressible diluent(s) followed by mixing with lubricant/glidant and subsequent compression. Direct compression utilises conventional manufacturing equipments, commonly available excipients, and requires the least time and efforts. Disintegrants and water soluble excipients are responsible for faster

disintegration/dissolution of the tablet. Some new coprocessed excipients have also been developed especially for FDTs for either providing two or more functionalities in a single excipient or improvements in functionality of excipient. Some of these coprocessed excipients are directly compressible and require, therefore, minimum processing steps in making FDTs and aid in achieving faster *in vivo/in vitro* disintegration/dissolution with sufficient hardness and friability.

Microcrystalline cellulose (MCC) is a diluent of choice for FDTs due to superior compatibility, drug carrying capacity and faster disintegration. Another important category of diluents is saccharides, which have been extensively used and explored in formulating FDTs, due to the availability of highly compressibility grades, low cost, aqueous solubility, and sweet and acceptable taste. Availability of MCC and saccharides in high compressibility grades has made direct compression as the method of first choice for manufacturing tablet. However, sometimes high compressibility of MCC or other excipient may adversely impact on disintegration of FDTs, but this problem can be solved with optimising the composition. It has been observed that most of the FDT formulations, meant for faster disintegration/dissolution, incorporate some saccharide as their necessary component.

2.1. Superdisintegrant Addition

Addition of large amounts of superdisintegrant(s) to a direct compressible tablet can fasten disintegration/dissolution of the tablet. In this approach, the type of disintegrant and its amount in the formulation are critically important. The most popular superdisintegrants used in formulating FDTs are croscarmellose sodium (CCS), sodium starch glycolate (SSG), crospovidone and low-substituted hydroxypropyl cellulose (L-HPC). Some less explored superdisintegrants are Indion 414, modified polysaccharides or gums, novel combinations like glycine-chitosan, chitosan alginate complex and *Plantago ovata* mucilage. MCC has been used in most of the formulations as multifunctional excipient, which act as diluent and disintegrant. Some of the literature reports on use of various disintegrants in directly compressed FDTs are provided in Table **1**.

Table 1. Use of superdisintegrants and various diluents in FDTs prepared by direct compression.

Drug	Diluent	Disintegrant	Ref.
Acetaminophen, ascorbic acid	MCC (Avicel PH-M series) and spherical sugar granules	L-HPC	[1]
Ascorbic acid and nifedipine	Mannitol	Crospovidone	[2]

CHAPTER 4

Moulding, Extrusion, Floss and Three Dimensional Printing Technologies for Developing Fast Dissolving/Disintegrating Tablets

Vikas A. Saharan*

Department of Pharmaceutics, School of Pharmaceutical Sciences, Sardar Bhagwan Singh Post Graduate Institute of Biomedical Sciences and Research, Balawala, Dehradun 248161, Uttarakhand, India

Abstract: This chapter describes various developments in the designing, fabrication and manufacturing of FDTs using various technologies based on moulding, extrusion, floss, and three dimensional printing (3DP). Moulding has evolved from conventional moulding/tablet triturates to heat moulding, moulding methods involving use of compressed gases or low boiling point solvents, microwave drying, vacuum drying and compression of wet granules in especially designed moulding machine. Extrusion is not yet fully explored for developing FDTs. Floss techniques has moved ahead from Shearform® floss through liquiflash to creation of microparticulates. Rapid prototyping techniques, especially three dimensional printing (3DP), have enabled the use of computer aided designing (CAD) possibilities in manufacturing of highly porous dosage form offering immediate and complex drug release characteristics, tablets of any shape and dosage forms which can flash into a matter of seconds.

Keywords: 3DP™, Compaction, Compression, Computer aided design, Cotton candy, EMP®, FlashDose®, Floss, Formulation, Free form fabrication, Heat moulding, Microwave drying, Press through package, Rapid prototyping, Shearform®, Tablet, TheriFlash®, TheriForm®, Vacuum drying, Wet compression.

1. INTRODUCTION

The moulded tablet or tablet triturate was originally introduced by Fuller in 1781 as oral unit dosage form made from moistened powder, comprising drug and excipients, pressed in to a cavity, extruded and dried [1, 2]. Commercially, the use

* **Corresponding author Vikas A. Saharan:** Department of Pharmaceutics, School of Pharmaceutical Sciences, Sardar Bhagwan Singh Post Graduate Institute of Biomedical Sciences and Research (www.sbspgi.edu.in), Balawala, Dehradun 248161, Uttarakhand, India; Tel: +91-135-2686246; Mobile: +91-843-9820796; Fax: +91-135-2686286; E-mail: vikas.pharmaceutics@gmail.com

Vikas Anand Saharan (Ed.)

of moulding had started in 1990s with the successful market launches of lyophilised tablets. Lyophilisation is also a moulding technique in which solvent is removed by sublimation. However, this chapter deals with techniques other than lyophilisation for removal of solvent from moistened or wet powder. Several other methods for removing solvents are drying in an air-circulating oven, vacuum drying and microwave drying. Additionally, compressed gases/low boiling point solvents can also be used in the making of moulded tablets from which the solvent is removed at normal temperature and pressure. Wet compression methods have also been employed for manufacturing wet tablets, which are dried later.

Extrusion is a less explored approach in making FDTs. However, its use in creating taste masked particulates/granules is widespread. These taste masked granules of bitter drugs have found their immense use in manufacturing FDTs having wide acceptability among paediatric/geriatric patients.

Sugar floss is prepared from a cotton candy machine by melting the sugar inside and forcing it to extrude through small holes resulting in floss fibres. These floss fibres can be chopped, mixed with other excipients, conditioned and subsequently compressed to obtain FDTs. Special machines have also been designed for preparing microparticulates, which can be incorporated into FDTs.

Rapid Prototyping (RP) technology, exemplified by three-dimensional printing (3DP), uses powder processing method and liquid binders to bind powders in multiple layers leading to the generation of a layer-by-layer three dimensional structure *via* programming in a computer. Various literature reports have highlighted the usefulness of 3DP in developing FDDFs and controlled drug delivery systems.

2. MOULDED TABLETS

Conventionally, water soluble excipients like lactose, mannitol, sucrose, dextrose or other appropriate diluents are used as base in preparing moulded tablets [1, 2]. Lactose remains the most frequently used base. Mannitol is preferred for additional sweetness, cooling and pleasant sensation in the mouth. Drugs that are incompatible with sugar/sugar alcohol may require other diluents like precipitated calcium phosphate, precipitated calcium carbonate, bentonite or kaolin. In the process of moulding, the tablet components are mixed with water and/or with an organic solvent in which at least one of the components partially dissolve to give stiff slurry, which can be formed into tablets by filling in moulds or using special machines. Most frequently, hydroalcoholic mixtures containing 50-80% alcohol

are used as solvent. Water content in solvent dissolves sugars and the resulting sugar solution acts as binder, while the alcohol speeds up the drying of the liquid. Water content can be reduced and sometimes completely eliminated, if tablet composition is water soluble. After shaping the tablet, the wet tablet is dried carefully. Evaporation of the solvent results in the binding of tablet components, whereby the tablets receive their strength. Fine hollow spaces remain after evaporation makes the tablet porous and penetrable to solvents for faster disintegration/dissolution. Conventional tablet triturates or moulded tablets provide satisfactory rate of dissolution but being too soft and brittle some difficulties may arise in packing and transporting due to practically pressure-less method of their production. The use of organic solvents may damage active ingredient, especially enzymes and indicators. Vapours of organic solvents require special provisions and safety measures in the production of the tablets. Water cannot be used as solvent for very readily water soluble drugs. When compared with conventional compressed tablets, moulded tablet suffers weight variation and content uniformity issues. Moulding methods have evolved with the development in science and technology to overcome some of these disadvantages. Moulded tablets have also gained great deal of attraction in recent years with the popularity and acceptability of FDTs among dysphagic, paediatric, geriatric, psychotic and frequently travelling patients. Compression moulding, heat moulding, moulding with the aid of compressed gas/low boiling point solvent, freezing with vacuum drying and microwave drying are some of the improvements which have been explored and employed for developing FDTs. Moulded tablets can be prepared by filling moulds with a dispersion of drug and excipients and subsequent drying of solvent by lyophilisation. However, this chapter deals with methods other than lyophilisation used in preparing moulded tablets.

2.1. Compression Moulding

Water soluble excipients are used in making moulded tablets because the resulting tablet is expected to dissolve rapidly and completely in mouth. Active ingredient is mixed with other water soluble excipients to obtain a uniform powder blend. Hydroalcoholic solvent is used to moist the powder blend followed by moulding of wet mass in moulding plates at a low compression pressure. Solvent from wet moulded tablet is removed by drying in air. Use of low compression pressure is helpful in maintaining desired porosity that is essential for quick disintegration/dissolution. Size of lactose (or other base material) particles, compression force, moisture content are some critical process parameters used for optimising tablets for quick disintegration/dissolution and adequate hardness. Poor mechanical strength of moulded tablets and masking undesirable bitter taste

CHAPTER 5

Patent Innovations in Fast Dissolving/ Disintegrating Dosage Forms

Kalpana Nagpal[1,*], Shailendra K. Singh[2] and **D. N. Mishra[2]**

[1] *Amity Institute of Pharmacy, Amity University, Noida, Uttar Pradesh 201303, India*

[2] *Department of Pharmaceutical Sciences, Guru Jambheshwar University of Science & Technology, Hisar125001, Haryana, India*

Abstract: The conventional oral drug delivery system, in spite of ease of administration and convenience of therapy, is associated with certain limitations especially for paediatrics, geriatrics, unconscious and travelling patients. To make the safe and effective usage of drugs, fast dissolving/disintegrating dosage forms (FDDFs) serves as an effective approach for rapid delivery of drugs. The present chapter is an effort to describe the various aspects of FDDFs including the different patented products and technologies, which are either commercially available in the market or in development pipeline. A systematic study of various patents related to formulation, packaging and evaluation of FDDFs is also provided. Thus, this chapter provides most comprehensive insights on different FDDFs technologies through their patents and innovative steps described therein.

Keywords: Advatab™, Disintegration, Dissolution, DuraSolv®, Dysphagia, Film, FlashDose®, Foamburst™, Frosta®, Lyoc™, Micap™, OraQuick®, OraSolv®, Proprietary, QuickSolv®, Soluleaves™, Superdisintegrant, Tablet, Technology, Trademark, Wafertab™, Wowtab®, Xgel™, Ziplets®, Zydis®.

1. INTRODUCTION

Drug delivery through oral route is a convenient and preferred route of administration. Solid dosage forms offer many advantages such as accurate dosing, stability, ease in manufacturing, small size of package and improved patient compliance [1], but they possess certain limitations like inconvenience or impracticability to be swallowed by paediatric (as their muscular and nervous systems are not fully developed), geriatric, dysphagic, psychiatric, travelling (no

* **Corresponding author Dr. Kalpana Nagpal:** Amity Institute of Pharmacy, Amity University, Noida, Uttar Pradesh 201303, India; Tel: +91-8447883427, E-mail: kalpananagpal@gmail.com, knchaswal@amity.edu

Vikas Anand Saharan (Ed.)

ready access to water), unconscious patients or nauseating and/or vomiting patients [1 - 7]. According to European Pharmacopoeia, "Orodispersible tablets are uncoated tablets intended to be placed in the mouth, where they disperse rapidly before being swallowed". The Center for Drug Evaluation and Research (CDER), US FDA defined Oral Disintegrating Tablets (ODT) as "A solid dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue." FDDF offer certain advantages over effervescent tablets, dry syrups and chewing gums/tablets. The administration of effervescent tablets/granules requires water, whereas, the chewing gums/tablets cannot be chewed by elderly patients and for paediatrics unpleasant taste reduces their acceptability, if the taste masking coat get ruptured during mastication [4]. Moreover, FDDF offer more accurate dosing to patients as compared to liquid dosage forms. Thus, FDDF offers certain advantages [4, 5, 8 - 12] as well as certain limitations [1, 4, 5, 8 - 12], which are discussed in earlier chapters. FDDF is a solid unit dosage form usually in the form of tablets, although orodispersible films and modified hard gelatin capsules are also available. This type of dosage forms disintegrate and/or dissolve rapidly in the saliva without chewing or requiring water to swallow. The FDA uses the term '*Orally Disintegrating Tablets*' to describe them, whereas, European Pharmacopoeia enlisted them as '*Orodispersible Tablet*' [1]. Moreover, these are also referred in many literature as Melt-In-Mouth Tablets, Fast Dissolving, Oral Disintegrating, Mouth Dissolving, Porous Tablets, Quick Dissolving or Rapid Disintegrating Tablets [4, 5].

Patents provide legal protection to inventor(s) for their inventions, which includes new medicines also. The inventor(s) must satisfy the three conditions, *i.e.* novelty, inventiveness (non-obviousness) and usefulness. In patenting, the inventor(s) is given a limited period of time of exclusivity, generally 20 years, to make and sell a product incorporating his/her invention. In return, to the inventor(s) make the invention public, thereby encouraging the continuation of scientific discovery. In this way, the inventor(s) can easily regain their significant investment in research and development. Such an activity acts as a fundamental incentive to innovative activities. The individuals also get recognitions for their creative idea and profitable reward for their marketable inventions. Such incentives encourage innovations and assure continuous improvements in the quality of human life. In nut shell, patents provide not only protection to the intellectual rights of researchers but also serve as an source of inspiration to future researchers [13, 14].

FDDFs cater to the needs of patients, formulation scientist as well as the manufacturer [15]. An improved version of the existing drug may come in the

market, especially for the drugs whose patent is about to expire. The market of the product will be extended exclusively, which in turn would benefit the manufacturer and has attracted lots of attention from the medium and large scale manufacturers of developing countries, who cannot afford heavy expenditure on search of new chemical entity.

2. PATENTED TECHNOLOGIES IN THE MARKET

2.1. Technologies in Fast Dissolving Tablets

The most common patented technologies used for formulating fast dissolving/ disintegrating tablets (FDTs) are briefly discussed hereunder [1, 4, 5, 16, 17]. The major advantages and the disadvantages associated with them are compared in Table **1**. Table **2** enlists some marketed products based on FDTs.

Table 1. A comparison of various patented technologies for FDTs.

Technology	Advantages	Disadvantages
Zydis®	• Light weight, eye pleasing, good to taste and touch product • Convenient and self preserving as final water content too low	• Expensive as freeze drying is involved and need special blister pack due to high fragile tablets • Poor stability • Maximum dose of water soluble drug is limited to approximately 60mg [27]
OraSolv®	• Two fold taste masking than Zydis® product • Low degree of compaction	• Appearance not too good like Zydis®; more brittle and weaker than conventional tablet
DuraSolv®	• Has durable product with higher mechanical strength than OraSolv® and can be packed in conventional blister pack • Faster and cost effective production • Structural integrity may be compromised with high dose of the drug Have fast disintegration time (<1 min) and hardness app.15-20 N	• Low drug loading capacity because the technology is not compatible with large dose of API • Not suitable for incorporation of taste masked coated pellets
Wowtab®	• Tablets so formed posses significant hardness and dissolution time; suitable for both conventional blister and bottle pack; more stable product than Zydis® or OraSolv® • Offers good taste as well as mouth feel and may incorporate various classes of drugs	• No significant change in bioavailability.
Flash Tab®	• Utilise most of the same excipients as in conventional tablets	-

CHAPTER 6

Excipients for Fast Dissolving /Disintegrating Tablets

Vikas A. Saharan*

Department of Pharmaceutics, School of Pharmaceutical Sciences, Sardar Bhagwan Singh Post Graduate Institute of Biomedical Sciences and Research, Balawala, Dehradun 248161, Uttarakhand, India

Abstract: Excipients play important functional roles in dosage form manufacturing. Disintegration and dissolution of dosage form and sometimes the active ingredient is greatly influenced by the use of excipient(s) like diluents and superdisintegrants in the formulation. With the advent of FDDF technologies, several directly compressible excipient systems have been introduced by excipient industry to ease fast disintegrating/dissolving tablet (FDT) manufacturing by the process of direct compression. These excipient systems have supplied a royalty free, licensee free and a low cost solution for FDT manufacturing to drug product manufacturers. Advancements in disintegrants and disintegration enhancers have also helped in formulating quicker disintegrating dosage forms. Some new excipients have been used to overcome bitter taste of drugs, improve compressibility of saccharides and as diluents in formulating FDTs. Some excipients have been modified and provided in special for their exclusive use in formulating FDTs. This chapter provides an updated review on some of the excipient/excipient for their potential use formulating FDTs.

Keywords: Diluent, Mannitol, MCC II, Microcrystalline cellulose, Parteck® ODT, Pharmaburst®, Polymer, Prosolv® ODT, Saccharides, Superdisintegrant, Taste masking.

1. INTRODUCTION

FDTs share same excipients which have been used in preparing conventional tablets. However, lyophilisation processes may require formulation of dispersion and thus excipients required are similar to those excipients which are used conventionally for making dispersions. This chapter provides a comprehensive

* **Corresponding author Vikas A. Saharan:** Department of Pharmaceutical Sciences, Sardar Bhagwan Singh Post Graduate Institute of Biomedical Sciences and Research (www.sbspgi.edu.in), Balawala, Dehradun 248161, Uttarakhand, India; Tel: +91-135-2686246; Mobile: +91-8439820796; Fax: +91-135-2686246; E-mail: vikas.pharmaceutics@gmail.com

view on selected categories of excipients, which are of considerable importance in achieving fast disintegration/dissolving properties in tablets. These excipients can be grouped into superdisintegrants, water soluble excipients and coprocessed excipients.

One of the important quality attributes to qualify the status of FDT for a tablet is its faster disintegration, which shall be less than 60 s as per USP or at the most 180 s as per European Pharmacopoeia. Addition of high amounts of superdisintegrant may achieve this faster limit of disintegration but with this problem of poor hardness and high friability may crop up. Hence quality by design concept shall be applied for optimising the mechanical strength of the tablet and faster disintegration properties. Various superdisintegrants, like crospovidone, sodium starch glycolate (SSG), croscarmellose sodium (CCS), low substituted hydroxypropylcellulose (L-HPC), *etc.*, have been used to induce faster disintegration in tablets. These superdisintegrants have found widely used in FDTs manufactured by direct compression, wet/dry granulation and compression-moulding methods.

When a matrix of water soluble excipients is compressed or compressed/moulded at low pressure, the resulting FDT will dissolve quickly in mouth due to soluble nature of fillers in the composition. Sugar based excipients have been widely employed for making quickly soluble rather than quickly disintegrating type tablets. Sweetness of these fillers also helps in masking bitter/saline or other obnoxious taste of the drug. Most of the sugar and sugar alcohols are non-compressible and their compression properties are required to be improved. Excipients manufacturers have seen the demand of drug product manufactures and accordingly provides various compressible grades of sugar based excipients.

Direct compression of tablets is very popular among drug product manufacturers due to the use of least number of processing steps in it. Hence, most of the diluents are now available in directly compressible grades. For making specialised tablets, like FDTs, coprocessed excipients have been manufactured, which can possibly avoid the transfer of costly proprietary/patented FDT technology, costly formulation development and time consuming in optimising formulations. Some coprocessed excipients require a single step of mixing API with lubricant/glidant and coprocessed excipient before compression to FDTs, *e.g.* Pharmaburst®, Parteck® ODT, Prosolv® ODT *etc*.

2. SUPERDISINTEGRANTS

Addition of large amounts of superdisintegrant(s) to a direct compressible tablet

can increase disintegration/dissolution of the tablet. In this approach, the type of disintegrant and its amount included in the formulation are of prime importance. The most popular superdisintegrants used for formulating FDTs are CCS, L-HPC, crospovidone and SSG. Some less explored superdisintegrants are Indion 414, modified polysaccharides or gums, novel combinations like glycine-chitosan, chitosan alginate complex and *Plantago ovata* mucilage. Some of the literature reports on use of various superdisintegrants in directly compressed FDTs are provided in Table **1**.

Table 1. Use of superdisintegrants and various diluents in FDTs prepared by direct compression.

Drug	Diluent	Disintegrant	Ref.
Acetaminophen and ascorbic acid	Avicel PH-M series and spherical sugar granules	L-HPC	[1]
Ascorbic acid and nifedipine	Mannitol	Crospovidone	[2]
Buspiron	Microcrystalline cellulose (MCC) (Avicel PH 102) and Pearlitol SD 200	Crospovidone, CCS and SSG	[3]
Carvidilol solid dispersion with PVP	MCC and mannitol	Crospovidone, SSG, CCS and polacrilin potassium	[4]
Celecoxib solid dispersion with sorbitol		SSG	[5]
Chlorpromazine HCl	MCC and mannitol	Crospovidone, CCS, SSG, L-HPC and pregelatinised starch	[6]
Cinnarizine	Avicel PH102 and mannitol	Crospovidone	[7]
Clonazepam	MCC and mannitol	Crospovidone, CCS and SSG	[8]
Clozapine	Avicel PH102 and mannitol	Kollidon CL and Explotab	[9]
Dicyclomine HCl, roxithromycin, montelukast sodium	Avicel PH102	Indion 414, CCS, SSG and crospovidone	[10]
Epinephrine	MCC (Avicel PH 301)	L-HPC	[11]
Ethenzamide	MCC	L-HPC	[12]
Famotidine	Spray dried lactose, mannitol and Avicel PH 101	SSG, Ac-Di-Sol and L-HPC	[13]
Famotidine	Dibasic calcium phosphate (DCP)	Ac-Di-Sol, crospovidone and SSG	[14]
Famotidine	MCC, xylitol and sucrose stearic acid esters	CCS	[15, 16]
Fexofenadine	Avicel PH102 and mannitol	Ac-Di-Sol, crospovidone and SSG	[17]
Flutamide	Ludipress, mannitol and Avicel PH102	SSG	[18]

CHAPTER 7

Taste Masking in Fast Dissolving/Disintegrating Dosage Forms

Vikas A. Saharan[1,*], **Vandana Kharb**[2] and **Anupama Singh**[1]

[1] *Department of Pharmaceutics, School of Pharmaceutical Sciences, Sardar Bhagwan Singh Post Graduate Institute of Biomedical Sciences and Research, Balawala, Dehradun 248161, Uttarakhand, India*

[2] *Sachdeva College of Pharmacy, Gharuan 140413, District Mohali, Punjab, India*

Abstract: Fast dissolving/disintegrating dosage forms (FDDFs) comprise dosage forms meant for dissolution/disintegration in saliva and subsequent swallowing of the formulation. FDDFs include fast dissolving/disintegrating tablets (FDTs), fast dissolving/disintegrating films (FDFs), fast dissolving/disintegrating pellets (FDPs) or fast dissolving/disintegrating granules (FDGs), *etc*. Drug release from such dosage forms starts from the oral cavity itself and, therefore, a part of total drug may be absorbed much before the drug reaches in the stomach. Early release of the drug in saliva, in close proximity to taste buds, makes it desirable that the drug shall be presented in a taste masked form and palatability shall be improved to an extent that dosage form is highly acceptable among patients. Therefore, bitter or other unpleasant taste of the drug is a great challenge to formulate a taste masked FDDF formulation. An ideal taste masking technique should provide a good refreshing mouthfeel, pleasant taste and appealing flavour. On the other hand, an ideal taste masking technique shall not impart grittiness, reduction in bioavailability and a large increase in the size of the dosage form. Approaches for taste masking are generally categorised into physical, chemical and organoleptic (physiological). The technology of taste masking is highly proprietary and extensively patented. Physical/chemical methods of masking the undesirable taste work synergistically with organoleptic approaches for improving the overall palatability of pharmaceutical formulations. Hence, several proprietary taste masking technologies utilise synergistic/additive effect of two or more approaches for taste masking. This chapter provides a comprehensive overview on taste masking methods, proprietary and/or patented technologies, giving special emphasis on their application in FDDFs.

[*] **Corresponding author Vikas A. Saharan:** Department of Pharmaceutics, School of Pharmaceutical Sciences, Sardar Bhagwan Singh Post Graduate Institute of Biomedical Sciences and Research (www.sbspgi.edu.in), Balawala, Dehradun 248161, Uttarakhand, India; Tel: +91-135-2686246; Mobile: +91-8439820796; Fax: +91-135-2686286; E-mail: vikas.pharmaceutics@gmail.com

Vikas Anand Saharan (Ed.)

Keywords: Adsorption, Aqueous solubility, Bitter, Bitterness threshold, Coating, Complexation, Cyclodextrin, Extrusion, Granulation, Microencapsulation, Multiple emulsion, Prodrug, Resin, Rheology, Salt, Solid dispersion, Taste inhibitor, Taste modifier.

1. INTRODUCTION

Taste masking approaches restrict the movement of bitter or other undesirable taste of the drug from the dosage form to the taste buds. However, complete/drastic restriction on drug release from dosage form may sometime pose additional issues like prolonging onset of action and reduction in bioavailability. Hence, in practice, dosage form is designed and optimised to have an adequate control on drug release without compromising rate and extent of absorption. Approaches for masking taste can be broadly classified in three categories: physical, chemical and organoleptic (physiological) [1]. Physical methods of taste masking use barrier approach in reducing the contact of the drug with taste receptors present in taste buds. Chemical approaches utilise complexation with cyclodextrins, ion-exchange resins (IER) and other excipients and ion-pairing, wherein the drug is housed or bound in a manner that release of the drug in the oral cavity is prevented and when such a complex reaches in stomach/intestine, complex breaks apart to make the drug available for absorption. Some other chemical approaches used in taste masking are formation of salts and prodrugs of bitter tasting drugs, which in turn are either poor water soluble or reduce interaction of drug with taste receptors. Organoleptic taste masking require use of sweeteners, taste modifiers and taste inhibitors/modifiers, which act on taste buds by either competing with the drug for receptor site or by desensitising taste buds or by providing their strong sweet sensation/taste by interacting with taste buds. Strong sweet taste and use of flavours produces overshadowing effect, which increases the palatability of the formulation. Use of sweeteners and flavours is an age old concept in taste masking, which is still applied in most of the formulations in addition to other physical and chemical methods. Drugs differ relatively on extent of bitterness/unpleasant taste and other physicochemical properties complicating the situation and thus no single approach of taste masking can be applied universally to all the drugs and to all the dosage forms. Optimisation studies are always required to find some best compositions to achieve acceptable masking of the bitter taste.

2. PHYSICAL APPROACHES

Physical modifications in formulations can mask the taste of unpleasant drug by either preventing the drug to interact with the taste buds or delaying the reach of

the drug to taste buds. These physical approaches of modifying formulations are also referred to as barrier methods. With these physical methods, the target of a formulation scientist is to reduce the drug release in oral cavity so that drug release shall remain lower than the bitterness threshold concentration. Bitterness threshold concentration can be identified for any bitter substance by organoleptic evaluation in human volunteers with a series of drug solutions varying in their concentrations. The highest drug concentration that does not elicit bitter taste is referred to as bitterness threshold concentration [2, 3]. A suitable control on drug release/dissolution of the drug from the formulation is used to maintain drug concentration lower than bitterness threshold concentration in the oral cavity. Physical approaches for reducing bitterness or other undesirable taste are coating, microencapsulation, granulations, solid dispersions, rheological modifications, microparticulates, multiple emulsions and adsorption.

2.1. Coating and Preparation of Microcapsules, Microspheres, Granules and Other Particulates

Applying polymer coating onto drug particles is an efficient mean of reducing the release of the drug below bitterness threshold in the oral cavity. Polymer coatings are applied on drug particles by spray coating in a pan or by fluidised bed coating. Alternatively, drugs may be incorporated into pellets, microspheres or microcapsules. These approaches allow the drug particles to be swallowed before attaining the threshold bitter concentration in the mouth. Coating and microencapsulation methods have disadvantages of a long term contact of drug with a liquid medium during manufacturing or storage at high humidity conditions, resulting in the release of a part of the drug in the liquid medium before the oral administration of the formulation. Furthermore, the applied polymer coat may weaken, soften, rupture or cracks may appear when coated drug particles or microcapsules are subjected to high pressures used in compressing tablets. Thus, it becomes an important pre-requisite to check whether the applied pressure is sufficient to withstand by microparticulates.

Coating/microencapsulation/granulation methods have been extensively used to overcome the problem of the unpleasant taste of the drug and render formulations palatable (Table **1**).

Table 1. Coating, microencapsulation and granulation methods for taste masking in FDDFs.

Drug	Taste Masking Method	Excipient/Polymer	FDDF and Preparation Method	Ref.
Acetaminophen	Fluidised bed coating	Kollicoat IR	FDT, dry coated tablets	[4]

CHAPTER 8

Quality Assurance and Evaluation of Fast Dissolving/Disintegrating Dosage Forms

Vikas A. Saharan*

Department of Pharmaceutics, School of Pharmaceutical Sciences, Sardar Bhagwan Singh Post Graduate Institute of Biomedical Sciences and Research, Balawala, Dehradun 248161, Uttarakhand, India

Abstract: Quality assurance and evaluation of fast dissolving/disintegrating dosage forms (FDDFs) require conduct of various pharmacopoeial and non-pharmacopoeial tests and their compliance to acceptance limits. Dosage forms specific and non-specific tests include assessment for hardness, weight variation, assay, content uniformity, friability, disintegration, dissolution, *etc*. Highly porous nature of fast disintegrating/ dissolving tablets (FDTs) makes them brittle and fragile. Friability limits for FDTs are generally higher than the friability limits of conventional tablets. Newer tests, methodologies and equipments have been devised for evaluation of *in vitro* disintegration/dissolution and to simulate *in vivo* conditions of the oral cavity. Drug dissolution/release studies are also required to be conducted in a manner so as to simulate *in vivo* oral conditions to ensure reproducibility of batches. The developed drug release tests and explored methodologies are correlated to *in vivo* disintegration/ dissolution for their wider acceptance and future incorporation in pharmacopoeia. Taste masking and palatability of FDDFs are evaluated during drug development and stability studies. Some of these evaluation tests have been incorporated in regulatory guideline and/or pharmacopoeia, while some others are in development phases. This chapter provides a comprehensive overview on various quality control/assurance tests for evaluation of FDTs and capsules.

Keywords: Capsule, Content uniformity, Disintegration, Dissolution, Drug release, FDT, Friability, Gamma-scintigraphy, Hardness, OD-mate®, ODT, ODT-101®, Palatability, Tablet, Taste, Texture analyser, Tricorptester®, Water absorption, Water content, Weight uniformity, Wetting time.

* **Corresponding author Vikas A. Saharan:** Department of Pharmaceutics, School of Pharmaceutical Sciences, Sardar Bhagwan Singh Post Graduate Institute of Biomedical Sciences and Research, Balawala (www.sbspgi.edu.in), Dehradun 248161, Uttarakhand, India; Tel: +91-135-2686246; Mobile: +91-8439820796; Fax: +91-135-2686286; E-mail: vikas.pharmaceutics@gmail.com

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INTRODUCTION

Fast Dissolving/Disintegrating Dosage Forms (FDDFs) are a group of dosage forms characterised by their quick *in vitro/in vivo* oral disintegration/dissolution and include tablets, mini-tablets, capsules, pellets, films, *etc*. Faster dissolution/ disintegration in the oral cavity has some obvious advantages like administration without water and ease and comfort in swallowing by special populations, *viz.* paediatrics, geriatrics, psychotics, bed-ridden patients, *etc*.

US FDA, CDER Nomenclature Standards Committee defines an orally disintegrating tablet (ODT) as "*A solid dosage form containing medicinal substances which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue*" [1]. US FDA guidance document on ODTs has defined the upper limits for disintegration time and weight of ODTs. ODTs must disintegrate in 60 s or less when evaluated by official tablet disintegration apparatus of USP or other equivalent methods [2]. However, alternative methods, which are more discriminating and proven correlations between *in vitro* and *in vivo* disintegration, may also be used. Several discriminating *in vitro* disintegration test methods for ODT with strong *in vivo* correlation and evaluation of ODT have come up. Ideally, weight of ODTs should not be greater than 500 mg. Tablets weighing more than 500 mg are difficult, however not impossible, to achieve faster disintegration and patient acceptance. ODTs have been formulated and reported with higher drug loading to benefit patients and still meet the ODT definition, safety and patient compliance requirements [3, 4]. The limit of 500 mg is frequently questioned by several authors and sponsors [3 - 5]. However, ODTs weighing more than 500 mg should be justified on the basis of their performance in disintegration and patient acceptance.

FDTs and Fast Disintegrating Capsules (FDCs) are evaluated for pharmacopoeial evaluation tests like uniformity of dosage units, friability, assay and disintegration/dissolution of the dosage form and dissolution/release of the drug from the dosage form. However, due to obvious differences in manufacturing technologies for FDTs from conventional tablet manufacturing, the acceptance limits for these tests are different from the acceptance limits for conventional tablets. Several modifications have been adapted in testing methodologies to assess faster disintegration/dissolution of FDDFs. Wetting test has been modified and simulated for evaluating wetting of FDTs in the oral cavity and correlated to *in vivo* disintegration. Due to rapid disintegration/dissolution of FDDFs in mouth, pharmacopoeial tests for disintegration and/or dissolution do not correlate well with *in vivo* disintegration/dissolution of the dosage form. Drug dissolution/

release studies have been modified and adapted so that they can correlate well to *in vivo* drug dissolution/release studies. Some successful dissolution test methods have found their acceptance in regulatory guidelines and pharmacopoeia. New equipments/machines have been developed and successfully commercialised for testing FDDFs. Rapid disintegration/dissolution in mouth, buccal/sublingual absorption and administration without water have led to the need for development of novel tests, different test methodologies and market launches of several novel disintegration test apparatuses for FDTs.

2. QUALITY CONTROL AND QUALITY ASSURANCE TESTS

2.1. Uniformity of Weight

Tablets contain a defined amount of the drug based on the daily dosing frequency. Uniformity of weight is an important quality control test to ensure that weight of tablets should not differ from permissible weight variations as defined in the official pharmacopoeia [6]. This test shall be carried out according to the official pharmacopoeial procedure [7]. Generally, uniformity of weight test is performed with 20 tablets, weighing each tablet individually, followed by estimation of their average weight and finally calculating percent variation of individual tablet from the average weight.

2.2. Potency and Content Uniformity

Potency and content uniformity of tablets are also assayed as per procedures recommended in the pharmacopoeia. It is evaluated by an assay procedure or a developed analytical procedure capable of extracting the drug from the dosage form. Evaluation of potency involves use of 20 tablets followed by crushing them together, extracting the drug from the powder mixture and subsequent analysing of the amount of drug present in mass equivalent to one dosage unit. Evaluation of content uniformity require test of individual tablet for drug content. Tablets having low dose of drug (25%/25 mg) are essentially subjected to uniformity of dosage units by evaluating their content uniformity [8]. ODMTs are essentially low dose dosage forms due to their small size and use of large amount of co-processed excipients. Low-dose and cohesive nature of drug pose may pose serious blend uniformity issues in powder blends leading to content uniformity issues. Therefore, FDTs of low dose drugs and ODMTs are compulsorily examined to comply with the requirements of content uniformity as per pharmacopoeia [9, 10].

CHAPTER 9

Clinical Studies on Fast Dissolving/Disintegrating Dosage Forms

Prashant Mathur[1,*], Arpita Jindal[1], Sokindra Kumar[2] and **Vikas A. Saharan[3]**

[1] *Department of Clinical Pharmacy, Division of Pharmaceutical Sciences, Shri Guru Ram Rai Institute of Technology and Science, Dehradun, Uttarakhand, India*

[2] *RV Northland Institute of Pharmacy, Greater Noida, Uttar Pradesh, India*

[3] *Department of Pharmaceutics, School of Pharmaceutical Sciences, Sardar Bhagwan Singh Post Graduate Institute of Biomedical Sciences and Research, Balawala, Dehradun, Uttarakhand, India*

Abstract: Swallowing medication has always been a major problem among 50% of the population, especially in cases of elderly and children due to a fear of choking, resulting to an inappropriate medication adherence and in turn to non-compliance of dosage regimen. Swallowing problems are also seen in adult people who are bed-ridden or those who are busy in working or travelling, which makes them to forget or miss their doses as it requires water to swallow. This issue can be overcome by using FDDFs (Fast Dissolving/Disintegrating Dosage Forms), which have gained an immense popularity worldwide and a specific position in the field of novel drug delivery systems due to their easier administration and excellent palatability. FDDF has characteristics of both solid as well as liquid dosage form, as during storage and before administration it is solid in nature, a stability factor and as soon as it is placed in the mouth or beneath the tongue it rapidly gets transformed into its liquid form in the presence of saliva within a few seconds of its administration. The buccal mucosa is well supplied with both vascular and lymphatic systems and most importantly avoidance of intestinal or hepatic metabolism. The site and extent of absorption through buccal cavity are the important factors to be considered in developing FDDFs. The other factors like meta-bolising enzyme transporters involved, bioavailability and physicochemical properties of the drug are also important properties to be considered in developing FDDFs. FDDFs, as delivery systems, are widely used in treatment of allergies or emergency conditions which require a rapid therapeutic effect of the drug, *e.g.* sublingual tablet of nitroglycerin in case of angina attack. The disintegration time is also the important factor for classifying a drug product as FDDF, as generally, it is below 60 s in case of FDDF. Several FDDF drug products belonging to Fast

* **Corresponding author Prashant Mathur:** Department of Clinical Pharmacy, Division of Pharmaceutical Sciences, Shri Guru Ram Rai Institute of Technology and Science, Dehradun, Uttarakhand, India; Tel: +91-135-2726435; Mobile: +91-7895221122; Fax: +91-135-2721762; E-mail: prashantmats@yahoo.com

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Dissolving/Disintegrating tablets (FDTs), Fast Dissolving/Disintegrating Oral Films (FDOFs) have been introduced in the market as a result of an increased patient demands and their market presence is expected to expand in the forthcoming years.

Keywords: Absorption, Bioavailability, Bioequivalence, Compliance, Clinical, Dysphagia, Film, Geriatric, ODT, Paediatric, Psychotic, Quality of life, Tablet.

1. INTRODUCTION

A drug delivery system is designed in a specific manner so that drug can reach to its target site or region in an appropriate concentration required to elicit desired therapeutic effect. Designing and developing a new drug or a drug delivery system has always been a tremendous challenge in the pharmaceutical industry [1]. Recently, the interest in designing the newer buccal route for drug delivery especially for metabolically unstable drugs has evolved drastically as the absorption of active ingredients from the oral cavity provides a direct passage for the drug into the systemic circulation [2]. Swallowing a tablet/capsule has been a major difficulty for paediatrics and geriatrics, leading to poor patient compliance. Dysphagia, *i.e.* difficulty in swallowing, is prevalent among all age groups [3]. According to a report, approximately 35% of the general population is suffering from dysphagia. Even 30-40% of elderly hospitalised subjects were found affected with some sort of dysphagia [4]. Size, surface, texture, odour and taste of tablets/capsules are the most frequent complaints for difficulty in swallowing. Paediatric and geriatric populations are more in need of conveniently swallowed dosage forms [5]. Some other studies have also revealed that majority of the population suffers from the problem of swallowing tablets or capsules [6]. These studies have shown an urgent requirement of novel dosage forms to overcome the problem of dysphagia. Easily dispersible dosage forms seem capable to overcome the problem of swallowing in paediatric and geriatric populations.

For the convenience of paediatric, geriatric and psychotic patients several FDDFs have been developed, *e.g.* FDDF would be a more suitable dosage form than antihistamine syrup for an 8-10 year old allergic child. Similarly, a woman of middle age with breast cancer undergoing radiation therapy would be more comfortable of placing the tablet beneath tongue or above the tongue for disintegration of tablet in the oral cavity [5]. Hence, FDDFs like FDTs, FDOFs may be most suitable choice for these patients [6]. FDDFs increase the patient compliance due to their quick disintegration/dissolution in the saliva within seconds and thereby eliminating the need of water for swallowing. These tablets, which can be placed in the mouth for their rapid dispersion/dissolution, are termed

as "Orodispersible" as per the European Pharmacopoeia [7] and "Orally Disintegrating Tablets (ODTs)" according to USP/NF [8].

Recently, FDDFs have gained immense popularity all around the world and the family of FDDF is continuously expanding with dosage forms like FDOFs, Fast Disintegrating Pellets (FDPs), Orally Disintegrating Mini-Tablets (ODMTs) and Fast Disintegrating Granules (FDGs). To enhance the quality of life (QOL) of patients, these new types of FDDFs are being developed and marketed by many pharmaceutical companies [9]. Ease of administration, no need of swallowing with water, accurate dosing, better palatability, rapid onset of action, avoidance of first pass metabolism and increased bioavailability are some of the potential advantages of FDDFs over other oral solid unit dosage forms [2, 10]. Furthermore, the advantages of oral route over other routes of administration are also gaining the acceptance of FDDFs among all types of patient populations. Thus, in the recent years a multiple number of fast dissolving over-the-counter (OTC) and prescription drugs have entered into the market worldwide. Nitroglycerin was the first drug that showed substantial amount of absorption through oral mucosa, after which several other drug delivery forms through oral cavity had been developed. The development of the buccal drug delivery systems can be differentiated into two periods of its invention. The first period focuses on the development of sublingual tablets and oral solutions. Recently, refined by using new technologies such as sprays, patches and quick-dissolving solid matrices, the second period of invention was spawned over the last decade with the innovations of using highly permeable oral mucosa for targeted drug delivery [2].

Despite their tremendous popularity, FDDFs are often being confused with other solid dosage forms present in the market, which can also be consumed without water such as lozenges, chewable tablets, *etc*. Lozenges are meant to dissolve slowly in the mouth, whereas chewable tablets require manual chewing before swallowing. FDTs are far more different from such type of tablets as they get rapidly dissolved/dispersed in the mouth in the presence of saliva few seconds. The research, development and marketing of these new unconventional dosage forms or delivery systems are been regulated by U.S Congress, which is been enforced by the U.S Food & Drug Administration (FDA). Through the Federal Register, FDA proposes rules and regulations for assisting the management of approval process for new drug and drug products, which are later compiled in the U.S. Code of Federal Regulations (CFR) [11]. The relevant CFR sections that address different aspects of clinical pharmacology and biopharmaceutics informational needs for supporting a new product's approval are Part 201 of Title

CHAPTER 10

Fast Dissolving Oral Films

Mahaveer Singh and **Hemant R. Jadhav***

Department of Pharmacy, Birla Institute of Technology and Sciences, Vidya Vihar, Pilani 333031, Jhunjhunu, Rajasthan, India

Abstract: Ease of administration and patient compliance makes the oral route as the most popular route of administration, but difficulty in swallowing or dysphagia may limit the use of oral route in special populations like paediatrics, geriatrics, psychotics, cancer patients, *etc*. Unavailability of water and episodic attack of allergy also contributes to difficulties in swallowing tablets and capsules. Here the novel fast dissolving oral film (FDOF) technology gives new hope to overcome these problems. Oral films made from active ingredient and hydrophilic polymers are capable of rapidly dissolution/disintegration in the buccal cavity. A part of the drug is absorbed from buccal route providing the advantages of quicker onset, bypassing first pass effect and reducing gastric degradation or metabolism. These qualities have made oral film a very popular and convenient dosage form for paediatric, geriatric as well as adult populations. This chapter describes formulation aspects, preparation technologies and some important patents of FDOFs.

Keywords: Dysphagia, Fast dissolving oral film, Mucoadhesive, Nitroglycerin, Pullulan, Starch.

1. INTRODUCTION

Historically, the most important route of administration has been the oral route. Since the start of drug dispensing, oral cavity has been used as a site for drug delivery for most of the drugs. Way back in 1847, it was discovered that nitroglycerin gets absorbed from the oral cavity. It was just a start because oral cavity has been exploited a lot for either local or systemic use. The FDOF is a new drug delivery system to provide easy administration of medicines to patients having problem in swallowing or patients suffering from nausea/emesis. Films can be used for their local application, rapid release of drugs in systemic circulation and in various mucoadhesive systems to give release in controlled

* **Corresponding author Hemant R. Jadhav:** Department of Pharmacy, Birla Institute of Technology and Sciences, Vidya Vihar, Pilani 333031, Jhunjhunu, Rajasthan, India; Tel: +91-1596-515506; Mobile: +91-94146-48696; Fax: +91-1596-244183; E-mails: hemantrj@gmail.com, hemantrj@pilani.bits-pilani.ac.in

Vikas Anand Saharan (Ed.)

fashion [1, 2]. FDOFs are more convenient to use when compared to other dosage forms such as tablets and capsules. FDOFs avoid swallowing of unnecessary water and acceptable taste and palatability can be obtained with easier dosing accuracy and better handling. Therefore, FDOFs have attracted lots of attention and many pharmaceutical companies have come up with FDOFs as their new drug products [3, 4].

The FDOFs offer various advantages over oral drug delivery systems, a few of the advantages are as follows:

- FDOFs can be used to deliver drugs sublingually and by buccal route. This improves the onset of action and dosing frequency thereby enhancing safety and efficacy of the drug.
- Oral films dissolve quickly than other oral dosages forms and are also more stable when compared to liquid or gel type preparations.
- Improved dosing accuracy can be obtained with oral films because each strip contains a fixed amount of the drug.
- Due to ease of administration, oral films offer advantage of improved patient compliance. It gives special benefit to paediatric, geriatric and patients suffering from neurodegenerative diseases, where proper and complete dosing is difficult.
- FDOFs dissolve rapidly in saliva eliminating the need of water to swallow the medication and thereby solves the problem of administering oral medications to patients suffering from swallowing disorders, especially patients suffering from nausea, particularly receiving cancer chemotherapy and to those who are suffering from drug induced nausea and vomiting.
- FDOF drug delivery technology allows pharmaceutical companies to extend revenue lifecycles of drugs vulnerable to generic competition.
- FDOF offers a convenient method of drug administration where drug is an abuse deterrent film matrix that cannot be crushed or injected by patients, thereby it prevents drug abuse.
- FDOFs are of immense use in cough, cold, sore throat and erectile dysfunctions, when an immediate onset of action is desired.

Challenges/disadvantages of FDOF are given below:

- Due to size limitations, FDOFs cannot be prepared for drugs having high dose.
- FDOFs, being hygroscopic, need proper storage conditions (*e.g.* dry place).
- For product stability and safety, specialised packaging may be required.

2. FORMULATIONS OF FAST DISSOLVING ORAL FILMS

2.1. Film Forming Polymers

Polymers are the most important constituents as they form the base for FDOFs. The polymer to be used in oral films should be free from toxic, irritant and leachable impurities such as nitrosamines. There should be sufficient peel, shear and tensile strength in the polymer [4]. It should be readily available at a cheaper cost. Films obtained should be tough enough to withstand damages during handling and transportation. Robustness of a film depends on polymer type and composition [5, 6]. Up to 45% w/w polymer can be accommodated in FDOFs. Most commonly used polymers are pullulan, gelatin, hypromellose, maltodextrin, *etc*. Non animal originated polymers are very important as they are suitable for vegetarians and people with religious dietary restrictions. Some of these polymers are discussed in following sections.

2.1.1. Natural Film Forming Materials

2.1.1.1. Pullulan

Pullulan is a natural polysaccharide consisting of maltotriose units. Three glucose units of maltotriose are connected by α-1,4 glycosidic bonds and maltotriose units are connected to each other by a α-1,6 glycoside bond (Fig. **1**). Bender *et al.* (1959) named it "pullulan." The chemical structure of pullulan was resolved in 1960 [7]. Bender and Wallenfels (1961) discovered the enzyme pullulanase, which hydrolyses pullulan and converts pullulan to maltotriose. The α-1,4 and α-1,6 linkage pattern imparts structural flexibility and solubility to pullulan, resulting in distinct film and fibre forming characteristics. Pullulan is produced from starch by the action of fungus *Aureobasidium pullulans*. Other microbial sources for producing pullulan from starches include *Tremella mesenterica*, *Cytaria harioti, Cytaria darwinii* [8], *Cryphonectria parasitica* [9], *Teloschistes flavicans* [10] and *Rhodototula bacarum* [11]. Pullulan provides clear homogeneous films without structural modification to it. Low oxygen permeability and low water content are characteristics which make it most suitable for production of thin films [12]. It is easily soluble in both hot and cold water and makes clear and viscous solutions. It has high adhesion and film forming abilities as compared to other polymers. Pullulan is a nonionic polysaccharide, which is blood compatible, biodegradable, non-toxic, non immunogenic, nonmutagenic and non carcinogenic. Pullulan films are thermostable and possess anti-static and elastic properties and can be developed

CHAPTER 11

Novel Fast Dissolving/Disintegrating Dosage Forms

Vikas A. Saharan*

Department of Pharmaceutics, School of Pharmaceutical Sciences, Sardar Bhagwan Singh Post Graduate Institute of Biomedical Sciences and Research, Balawala, Dehradun 248161, Uttarakhand, India

Abstract: Fast disintegrating tablets (FDTs) were initially developed for immediate drug delivery, quicker onset of action and as age appropriate dosage form for special populations like geriatrics, paediatrics, psychotics, *etc*. Their quick dissolution/ disintegration in the oral cavity has made them suitable for incorporating microparticles/pellets for developing controlled drug delivery systems. Furthermore, advancement in manufacturing technologies and dosage forms have led to the introduction of newer dosage forms like oral disintegrating mini tablets (ODMTs), fast disintegrating capsules (FDCs), fast disintegrating pellets (FDPs) and orodispersible or to dissolve in oral powders. ODMTs are small size (2-3 mm in diameter) tablets prepared with characteristics of faster dissolution/disintegration. ODMTs have been found suitable and well acceptable in children. Perforation and vacuum drying methods have been used to convert traditional capsules into FDCs to overcome disadvantages of other FDDFs like expensive manufacturing, low payload, lengthy processes and insufficient masking of undesirable taste. Extrusion spheronisation and spray coating of drug with suitable excipients can led to FDPs, while orodispersible/effervescent powders can be filled in a unit dose packing. This chapter details about these novel FDDFs *vis a vis* to some novel advancements in their compositions.

Keywords: Capsules, Controlled release, Drug targeting, Granules, Mini tablets, Oral disintegration, Pellets, Powders.

1. INTRODUCTION

FDTs have been extensively explored for their advantages like ease of administration, wide acceptability, popularity and clinical advantages. Several new dosage forms in the family of FDDFs have emerged with time. Some of these have successfully reached to the market, while some others are in the final phases

* **Corresponding author Vikas A. Saharan:** Department of Pharmaceutics, School of Pharmaceutical Sciences, Sardar Bhagwan Singh Post Graduate Institute of Biomedical Sciences and Research (www.sbspgi.edu.in), Balawala, Dehradun 248161, Uttarakhand, India; Tel: +91-135-2686246; Mobile: +91-8439820796; Fax: +91-135-2686286; E-mail: vikas.pharmaceutics@gmail.com

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of development. FDCs, ODMTs, FDPs and orodispersible/effervescent powders in a stick are some novel FDDFs. Table **1** provides some recent development attempts with some novel FDDFs.

Table 1. Recently developed novel FDDFs.

Drug	Important Excipients	Method/ Technology	FDDFs	Remarks	Ref.
—	Hard gelatin/HPMC capsules (size 1), microcrystalline cellulose (MCC) (Avicel PH101 and PH112), mannitol, lactose monohydrate, saccharose and maize starch	Vacuum-drying or perforating conventional hard capsules	FDCs	Disintegration time of perforated capsules (6–10 holes of diameter 25–50 mm) was 39 s. Vacuum-dried brittle capsules disintegrated orally in 7.1±4.8 s.	[1]
—	Hard gelatin capsules, PEG, HPMC capsules, gelatin (type B) granules with different bloom strengths (43, 80, 100, 180 and 260), polyethylene glycol (PEG) 400, 1500 and 4000, cross-linked sodium carboxymethyl cellulose (SCMC), Ac-Di-Sol®, Avicel® PH101, Tylopur® C600, Explotab®, sorbitol, xylitol, d(+)-lactose monohydrate, citric acid and saccharose	Optimised dipping process	Fastcaps (FDCs)	Decreasing bloom strength of gelatin and adding sugars or PEGs reduced disintegration time.	[2]
Hydrochlorothiazide	Parteck® ODT, Ludiflash®, Pearlitol® Flash, Prosolv® ODT, Pharmaburst® 500, magnesium stearate and Pruv®	Direct compression in tablet machine equipped with a mini-tableting tool (Euro-B 19-tip) and power feeder	ODMTs	Novel dosage forms for children with advantages of ease of administration, flexible dose measurement and use of safe excipients	[3]

(Table 1) contd.....

Drug	Important Excipients	Method/ Technology	FDDFs	Remarks	Ref.
Dextromethorphan HBr monohydrate	Amberlite® IRP69, ethylcellulose and Aquacoat® ECD, Surelease®, Kollicoat® SR30D, Mannogem™ EZ Spray and spray dried mannitol	IER drug complexes by batch process; polymer coating by Wurster process and high shear wet granulation process	Sustained release FDTs	Diffusion governed drug release; drug release followed Higuchi and Boyd model	[4]
Model bitter drug	Amberlite® IRP69, Eudragit® RS, Eudragit® RL, triethyl citrate, talc, mannitol, Ac-Di-Sol®, citric acid, sodium bicarbonate and magnesium stearate	Coated drug-resin complexes were compressed to tablets	Sustained release FDTs	Taste masking and sustained release properties of IER and fast disintegration/ dissolution of FDTs coupled in a single dosage form	[5]
Ibuprofen	Phospholipon® 80H, Lipoid® S75, Kollicoat® SR 30D, Kollidon® 90F, Amprac® 01, Eudragit® RD 100, Explotab®, Kollidon® CL, aspartame, Pearlitol® SD200 and magnesium stearate	Granulation; aqueous polymer pan coating; simple compression technology to prepare FDT	Fast dispersible slow releasing FDT	Reduction of gastric side effects	[6]
Nicorandil	Myristyl alcohol and stearyl alcohol		Dry emulsion loaded FDT	*In vitro* release of nicorandil sustained over 6 h from FDT	[7]
Ketoprofen	Eudragit® RS-30D, Starch 1500®, PEG 6000, lactose, mannitol and polyvinylpyrrolidone	Spray drying followed by direct compression	Sustained drug release FDTs	*In vivo* pharmacokinetic studies exhibited significant extended release profile	[8]
Paracetamol and theophylline, riboflavin	Pectinic acid and MCC Sanaq® 102 G	Extrusion spehronisation	FDPs	Pectinic acid (10% methoxylation) was used as an extrusion aiding excipient	[9]
Theophylline monohydrate	MCC II (MCC Sanaq® Burst)	Extrusion spehronisation	FDPs	A storage humidity of 55-80% was recommended to maintain faster disintegration/dissolution	[10]

CHAPTER 12

Approved and Marketed Fast Dissolving/ Disintegrating Drug Products

Vikas A. Saharan[1,*], **Anupama Singh**[1] and **Vandana Kharb**[2]

[1] *Department of Pharmaceutics, School of Pharmaceutical Sciences, Sardar Bhagwan Singh Post Graduate Institute of Biomedical Sciences and Research, Balawala, Dehradun 248161, Uttarakhand, India*

[2] *Sachdeva College of Pharmacy, Chandigarh-Ludhiana National Highway, Gharuan 140413, Punjab, India*

Abstract: Websites of various drug regulatory agencies like US FDA, EMA, MHRA, PMDA and CDSCO were visited and information about approval and market authorisations of FDDF drug products' was collected with an aim to provide updated lists. Additionally, information about marketed FDDF drug products was also retrieved from websites of pharmaceutical companies and other literature sources. This chapter comprehensively enlists various drug products approved and marketed in US, UK, Europe, Japan and India.

Keywords: Bioequivalence, Brand, CDSCO, Controlled release, EMA, FDA, Film, Generic, MDT, MHRA, Mouth dissolving, ODT, Orally disintegrating, Orange book, Orodispersible, Patent, PMDA, Proprietary, Tablet.

1. INTRODUCTION

From regulatory context, FDDF products are regarded as novel drug delivery systems, which require bioequivalence testing with their equivalent conventional dosage forms. Immediate release drug products shall be tested for bioequivalence with reference listed conventional drug products, if the FDDF product is first market entry. If any FDDF product is already available in the market, the new product (generic FDDF) shall be compared to the reference listed FDDF product. So, bioequivalence testing of a FDDF is an essential criterion for market entry of FDDF product of an approved drug. Bioequivalence of a FDDF product is

[*] **Corresponding author Vikas A. Saharan:** Department of Pharmaceutics, School of Pharmaceutical Sciences, Sardar Bhagwan Singh Post Graduate Institute of Biomedical Sciences and Research (www.sbspgi.edu.in), Balawala, Dehradun 248161, Uttarakhand, India; Tel: +91-135-2686246; Mobile: +91-8439820796; Fax: +91-135-2686246; E-mail: vikas.pharmaceutics@gmail.com

assessed by either pharmacokinetic or pharmacodynamic methods.

As per EMA guidelines, BCS biowaiver for FDDF product is considered only if the API is not absorbed in mouth [1]. However, there is an ongoing debate and several research reports have advocated use of *in vitro* testing of bioequivalence by performing dissolution studies in small volumes (*i.e.* 5 mL of volume) of dissolution studies, which can resemble the dissolution in mouth and thus suggested requirement to amend BCS solubility criterion for FDDFs like Orally Disintegrating Tablets (ODTs), Fast Disintegrating/Dissolving Tablets (FDTs), Fast Dissolving Oral Films (FDOFs), buccal and sublingual tablets [2]. A standardised bioequivalence protocol require FDDF products to be administered orally only after prior wetting of the mouth with 20 ml of water and a limitation of not taking water within 1 h of administration.

Various generic FDDF products have entered in the market to compete the success of patented FDDF products. FDDF Drug market is continuously expanding with the rise of regulatory requirements and increase in awareness of drug products for paediatrics, geriatrics and other special populations. Newer technologies are continuously emerging to shape a tablet or other dosage form meant for faster disintegration/dissolution. Pioneer technologies of manufacturing FDDF utilise process control to optimise disintegration/dissolution. New technologies have emerged, which controls crystal growth and porosity while utilising the conventional manufacturing processes in shaping tablets. The latest technological innovations involve the application of prescription design type approaches in formulating FDDF products. New fabrication method like 3-dimensional printing is also gaining access from research and development sections through pilot plant to manufacturing sections of pharmaceutical industries.

GlaxoSmithKline's Zofran® ODT (ondansetron) and Lilly's Zyprexa® Zydis® (olanzapine) are two commercially successful products, which have motivated the entry of generic FDTs [3]. However, Zyprexa® Zydis® formulation still enjoys marketing exclusivity till 7/26/2016 in US [4]. FDT market is expected to reach $12 billion globally by 2018 with the popularity and growth of FDTs in various developing countries. FDOF market is expected to reach $1 billion in 2015 [5]. FDDF market is also expanding with introduction of newer products like sustained/controlled release FDTs, which have been successfully launched. Development pipeline of FDDF products is also increasing parallel with other novel dosage forms like FDGs, FDPs, and ODMTs.

2. PROPRIETARY TECHNOLOGY BASED FDDF PRODUCTS

Various proprietary technologies for making FDTs are provided in Table **1** and successful marketed products based on these technologies are presented in Table **2** and Table **3**. Table **4** provides proprietary FDOF technologies and list of companies, which have successfully marketed their FDOF products. A list of marketed FDOF product is provided in Table **5**. Most of these FDDF technologies (Table **1** and Table **4**) are invented and patented in US, Europe and Japan. However, a few technologies have been developed in other countries but lack of aggressive marketing/licensing has resulted in only limited regional success.

Table 1. Various proprietary FDT technologies.

Proprietary FDT Technology	Company	Website	Technology Platform
Zydis®, Zydis® Ultra, Zydis® Nano, Zydis® Bio	Catalent	www.catalent.com	Lyophilisation
Lyoc®	Cima Labs	www.cimalabs.com	Lyophilisation
QuickSolv®	Jenssen	www.janssenpharmaceuticalsinc.com	Lyophilisation
Pharmafreeze®	SPI Pharmaceuticals	www.spipharma.com	Excipient system for lyophilisation
OraSolv®/DuraSolv®	Cima Labs	www.cimalabs.com	Compressed tablet
Flashtab®	Ethypharm	www.ethypharm.com	Compressed tablet
Wowtab®, Wowtab-Wet®, Wowtab-Dry®	Astellas (Yamanouchi)	www.astellas.com	Low pressure compression moulding
FlashDose®	Valeant (Biovail)	www.valeant.com	Sugar floss
OraQuick®	Perrigo	www.perrigo.com	Compressed tablets
Solblet®	Kyowa Hakko Kirin	www.kyowa-kirin.com	Compressed tablet, external lubrication
Advatab®/Ziplets	Aptalis (Eurand)	www.aptalispharma.com	Compressed tablet, external lubrication
Ziplets®	Aptalis (Eurand)	www.aptalispharma.com	Compressed tablet
Pharmaburst®	SPI Pharmaceuticals	www.spipharma.com	Excipient system for direct compression
SUITAB®, SUITAB-NEX®, SUITAB-MAX®, SATAB®, PEATAB®	Dainippon Sumitomo Pharma	http://www.ds-pharma.co.jp	Compressed tablet

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VIKAS ANAND

Vikas Anand Saharan is the Professor and Head of the Department of Pharmaceutics, School of Pharmaceutical Sciences, Sardar Bhagwan Singh Post Graduate Institute of Biomedical Sciences and Research (SBSPGI), Dehradun (India). He did B. Pharm. from SBSPGI Dehradun, masters from NIPER Mohali and Ph.D. from Mohanlal Sukhadia University Udaipur. He has 15 years of teaching and research experience in Pharmacy, and has published 46 Papers in journals, presented 50 papers in conferences, supervised 21 M.Pharm. thesis and is currently supervising 5 Ph.D. students. He has 2 books and 1 book chapter to his credit. His biography has been published in Marquis Who's Who in the World" 2009-2016th editions. He was the topper of B.Pharm., awarded NIPER fellowship and honour award for GATE guidance. He is the editor-in-chief of 01 journal, editorial board member of 26+ journals and a peer-reviewer of 20+ journals. He is a CPCSEA nominee, innovator of PSOAR and PGIAR custom search engines and a life member of APTI, APA-IDMA, LASA, and InPharm Association. He is a registered pharmacist at Rajasthan Pharmacy Council. He is the recipient of grant-in-aid under AICTE-MODROBS project.