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Review Article

Fixed dose combination products as Oro-dispersible tablets: A review

C. Gothainayaki, A.N. Rajalakshmi*

College of Pharmacy, Mother Theresa Post Graduate and Research Institute of Health Sciences, Puducherry, India.

ABSTRACT

A fixed-dose combination (FDC) drug is a one that includes two or more active pharmaceutical ingredients (APIs) combined in a single dosage form, which is manufactured and distributed in fixed doses [1]. It increases patient compliance by reducing the no. of medications that a patient has to take especially for geriatric and pediatric patients. Orally disintegrating tablets (ODTs) are solid dosage forms containing a medicinal substance or active ingredient that rapidly disintegrates upon contact with saliva, typically within 30 s, eliminating the need for swallowing. It also increases patient compliance by reducing the swallowing problems faced by the patients especially for geriatric and pediatric patients. This review is about combining the techniques of both FDC and ODT formulations which promises to have a wide range of advantages to pediatric and geriatric populations, institutionalized and psychiatric patients, those suffering from nausea and vomiting, and individuals with lack of access to water. In spite of these advantages rarely do we find FDC-ODT products in our commercial market, this review aims at analyzing all the aspects of FDC and ODT formulations thereby forming the foundation for further studies.

Keywords: Fixed-dose combinations, Orally disintegrating tablets, Patient compliance.**Article Info:** Received 24 Jan 2019; Review Completed 17 March 2019; Accepted 18 March 2019; Available online 20 March 2019

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*Address for Correspondence:

Dr. A.N. Rajalakshmi, HOD, Department of Pharmaceutics, College of Pharmacy, Mother Theresa Post Graduate and Research Institute of Health Sciences, Puducherry, India.

INTRODUCTION

FDC:

Initially, fixed-dose combination drug products were developed to target a single disease (such as with antiretroviral FDCs used against AIDS). However, FDCs may also target multiple diseases/conditions, such as Caduet (atorvastatin/amlodipine) or Exforge (amlodipine/valsartan). In cases of FDCs targeting multiple conditions, such conditions might often be related—in order to increase the number of prospective patients who might be likely to utilize a given FDC product. This is because each FDC product is mass-produced, and thus typically requires having a critical mass of potentially applicable patients in order to justify its manufacture, distribution, stocking, etc.² It is therefore safe to say that the FDCs have more advantages when there is an identifiable patient population for whom treatment with a particular combination of actives in a fixed ratio of doses has been shown to be safe and effective, and when all of the actives contribute to the overall therapeutic effect. In addition there can be real clinical benefits in the form of increased efficacy and/or a reduced incidence of adverse effects, but such claims should be supported by evidence.

Definition: The Food and Drug Administration, USA defines a combination product as 'a product composed of any combination of a drug and a device or a biological product and a device or a drug and a biological product or a drug, device, and a biological product'³

Combination Rule: The primary guiding principle for the approval of FDC products is the combination rule as described in FDA's guidance for development of FDC and co-packaged drug products as well as in 21CFR 300.50, which describes FDA's policy on the approval of FDC products for humans. This rule states that "Two or more drugs may be combined in a single dosage form when each component makes a contribution to the claimed effects and the dosage of each component (amount, frequency, duration) is such that the combination is safe and effective for a significant patient population requiring such concurrent therapy as defined in the labeling for the drug."⁴

Synonyms: Combopill, Polypill.²

ADVANTAGES

1. Offers improved compliance and convenience to patients and prescribers.

2. The cost of an FDC finished pharmaceutical product (FDC-FPP) may be less than that of separate products given concurrently.
3. Improves patient adherence and reduces the development of resistance in the case of antimicrobials.
4. Simplifies the logistics of procurement and distribution.

DISADVANTAGES

1. FDCs are less likely to be useful under the following circumstances.
 - a) Either the doses of the components, and/or the ratio of doses, typically differ from patient to patient.
 - b) Patients are likely to be taking different doses at different stages of treatment (for example initial treatment compared with long-term treatment).
 - c) Dose adjustment is necessary in special populations, such as in people with renal or hepatic impairment.
2. The resulting FDC product may be so large that patients find it difficult to swallow.
3. Dosage alteration of one drug is not possible without alteration of the other drug.⁵
4. Differing pharmacokinetics of constituent drugs pose the problem of frequency of administration of the formulation.⁵
5. By simple logic there are increased chances of adverse drug effects and drug interactions compared with both drugs given individually.⁵
6. If an adverse drug reaction occurs from using an FDC, it may be difficult to identify the active ingredient responsible for causing the reaction.²

For a successful development of a new FDC product there must be a balance between these advantages and disadvantages. A proper way for going about this is listing and discussing them based on scientific and medical principle.

PROPERTIES ESSENTIAL FOR AN FDC PRODUCT

1. There must be a medical rationale in combining two or more active pharmaceutical ingredient. For example,
 - a) For antimicrobials, the combination should result in a reduced incidence of resistance.
 - b) In the case of some antiviral drugs, one drug should act as a booster for another.

2. The component actives must have compatible pharmacokinetics and/or pharmacodynamics (i.e.) it should remain unchanged when combined into a FDC product.
3. The FDC product must be bio-equivalent to the individual products of similar strengths.
4. The drugs in the combination should act by different mechanisms.⁵
5. It must provide better reliability and patient adherence than all of the components as loose combinations of single entity products
6. There must be an identifiable patient group for which this combination of actives and doses is suitable therapy. The larger the patient group in question, the more significant is this factor.
7. The incidence of adverse reactions in response to treatment with the combination must be lower than in that response to any of the component actives given alone, for example as a result of a lower dose of one component or a protective effect of one component, and particularly when the adverse reactions are serious. The combination should not have supra-additive toxicity of the ingredients.⁵
8. The active pharmaceutical ingredients in the combination must be chemically and physico-chemically compatible, or special formulation techniques must have been used that adequately addresses any incompatibility.
9. The cost of the combination as compared with the cost of individual components must be taken into account.

However, issues of cost and procurement alone are not sufficient reason to approve an FDC if it has not been justified by appropriate data and on scientific and medical principles.

ADDRESSING THE IRRATIONALITY PROBLEMS ASSOCIATED WITH FDC PRODUCTS

It is no secret that our health system today has fallen prey to a number of irrational FDC products. Many products are being manufactured and marketed without any medical rationale behind it. This is a major concern because these products expose patients to unnecessary risk of adverse drug reactions. Some of the products that were proven to be irrational and the reasons for their irrationality are given below.

Table 1: Drug combinations and their irrationality ⁷:

S.N.	Drug combinations	Irrationality
1.	Norfloxacin + Metronidazole; Norfloxacin + Tinidazole; Norfloxacin + Tinidazole + Loperamide	Though claimed to be broad spectrum, combining (antiamoebic) with fluoroquinolone (antibacterial) is irrational because patient suffers only from one type of diarrhoea. Using this combination adds to cost, adverse effects and may encourage resistance.
2.	Nimesulide + Diclofenac; Nimesulide + Dicyclomine + Simethicone; Nimesulide + Paracetamol;	Nimesulide a controversial drug, has been banned in many countries. It is a sorry state of affairs that its combinations are readily available over the counter. Combining two NSAIDs may increase the side effects of both the NSAIDs. There is little documentary evidence that a preparation containing more than one analgesic is more effective than a single ingredient preparation.
3.	Amoxycillin + Cloxacillin	Amoxycillin is inactive against staphylococcus, as most strains produce β -lactamase and cloxacillin is not so active against streptococci. For any given infection, one of the components is useless but adds to cost and adverse effect. Since amount of each drug is halved, efficacy is reduced and chances of selecting resistant strains is increased.
4.	Domperidone + Rabeprazole; Domperidone + Esomeprazole	Increased incidence of rhabdomyolysis.
5.	Enalapril + Losartan	Combining two drugs affecting the same pathway is irrational; it doesn't add to efficacy.

In an attempt to stop the irrational use of FDCs, the Union Health Ministry banned the manufacture, sale or distribution of 328 varieties of FDC drugs for human consumption. Thus it is important that there must be a proper risk-benefit assessment carried out before the manufacture of FDC products. The risk must not outweigh the benefits of FDCs.

FORMULATIONS IN WHICH FDC PRODCUTS ARE AVAILABLE

- Tablet
- a) Film coated tablet
- b) Bilayered tablet
- c) Trilayered tablet
- d) Tablet in tablet
- e) Coated beads in tablet

- f) Chewable tablet
- g) Dispersible tablet
- Capsules
- a) Capsule in capsule
- b) Beads and powder in capsule
- c) Coated beads in capsule
- d) Coated powder in capsule
- Topical preparations and Transmucosal preparations
- Injectables and Inhalations
- Syrup and Suspension
- Ear and eye drops

Table 2: List of a few examples of the available FDC products (US-FDA approved) ⁸.

Active ingredient	Proprietary name	Category	Strenght
Sulfamethoxazole, Trimethoprim	Sulfatrim –SS	Anti-infective Agents - Antibiotics	800mg, 160mg (or) 400mg, 80mg
Reserpine, Trichlormethiazide	Metatensin #2	Antiadrenergics, Diuretics	0.1mg, 2mg
Pyrimethamine, Sulfadoxine	Fansidar	Antimalarials	25mg, 500mg
Oxytetracycline hydrochloride, Polymyxin B Sulfate	Terramycin-Polymyxin	Antibiotics	EQ 100mg Base, 1,00,000 Units
Naloxone Hydrochloride, Pentazocaine hydrochloride	Talwin NX	Analgesics -Opioid antagonist	EQ 0.5mg Base, EQ 50mg Base
Metformin Hydrochloride, Rosiglitazone Maleate	Avandamet	Anti-diabetics	500mg, EQ 1mg Base (or) 1g EQ 2mg Base
Magnesium Hydroxide, Omeprazole, Sodium Bicarbonate	Zegerid	Laxative, Anti-ulcer, Antacid	700mg, 20mg, 600mg (or) 700mg, 40mg, 600mg

Applications

- FDCs are particularly useful in the management of HIV/AIDS, malaria and tuberculosis, which are considered to be the foremost infectious disease threats in the world today.

Specific Evaluation Tests

- Bioequivalence Testing:** In general, the bioequivalence guidelines for FDCs are fundamentally similar to those for products containing a single API. In other words, the rate and extent of absorption of each active from FDC should not be significantly different, respectively, from the rate and extent of each active from individual mono-products. In spite of subtle differences in BE criteria among various agencies, the common critical pharmacokinetic parameters are AUC_{0-t} , $AUC_{0-\infty}$, and C_{max} in studies to determine bioequivalence after a single dose. For these parameters, the 90% confidence interval for the ratio of the FDC (test) and individual mono-products (references) should be contained within the acceptance interval of 80.00–125.00% . ^{9, 10}

ODTs

Orally disintegrating tablets (ODTs) are solid dosage forms containing a medicinal substance or active ingredient that rapidly disintegrates upon contact with saliva, typically within 30 s, eliminating the need for swallowing. ODTs are a new generation of formulations which combine the advantages of both liquid and conventional tablet formulations, and at the same time, offer added advantages

over both the traditional dosage forms. They provide the convenience of a tablet formulation and also allow the ease of swallowing provided by a liquid formulation. Thus it greatly improves compliance for patients suffering from dysphagia (difficulty in swallowing), a condition estimated to affect as much as 50% of the population. Dysphagia is particularly prevalent in pediatric and geriatric populations, institutionalized and psychiatric patients, those suffering from nausea and vomiting, and individuals with lack of access to water. ¹²⁻¹⁵

Initially ODT products entered the market in the 1980s, after which its demand has only grown steadily. Oral route has always been the most preferred route of administration to patients for decades because of the several advantages and high patient compliance. Among the oral route tablets and hard gelatin capsules constitute the major portion. However, many patient groups such as the elderly, children, and patients who are mentally retarded, uncooperative, nauseated, or on reduced liquid-intake/diets have difficulties swallowing these dosage forms. Those who are traveling or have little access to water are similarly affected. ODTs are considered superior dosage forms than tablets and capsules because it overcomes several of these disadvantages by disintegrating rapidly in saliva, usually in a matter of seconds, without the need to take it water and thus avoiding swallowing difficulties. Thus many research scholars were encouraged and interested to conduct studies to find out different possibilities and approaches in the generation of ODTs.

When put in the mouth, these dosage forms disintegrate instantly to release the drug, which dissolves or disperses in the saliva.¹⁶ Thereafter, the drug may get absorbed from the pharynx and esophagus or from other sections of GIT as the saliva travels down. In such cases, bioavailability is significantly greater than that observed from conventional tablet dosage form.¹⁷

ODTs are distinguished from conventional sublingual tablets, buccal tablets, and lozenges, which require more than a minute to dissolve in oral cavity.¹⁸

Figure 1 Absorption of drug from an intact tablet.

Definition: The US Food and Drug Administration Center for Drug Evaluation and Research (CDER) defines, in the 'Orange Book', an ODT as "a solid dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue"²⁰. The significance of these dosage forms is highlighted by the adoption of the term, "Orodispersible Tablet", by the European Pharmacopoeia which describes it as a tablet that can be placed in oral cavity where it disperses rapidly before swallowing.²¹

Synonyms: Fast melts, Quick melts, Fast disintegrating, Orodispersible systems, orodisperse, mouth-dissolving, quick-dissolve, freeze-dried wafers, rapimelts, melt-in-mouth tablets and rapid dissolving table.²²⁻²⁶

Advantages: 17, 18

1. Patients with difficulty in chewing and swallowing (dysphagia) can use these ODTs tablets easily. Thus the risk of choking or suffocation during oral administration of conventional formulations due to physical obstruction is avoided²⁷
2. Since there is no water requirement for swallowing purpose it is suitable during traveling, where water may not be available¹⁷
3. Drug dissolution and absorption as well as onset of clinical effect and drug bioavailability may be significantly greater than those observed from conventional dosage forms¹⁷
4. ODTs can be used easily in children who have lost their primary teeth but do not have full use of their permanent teeth¹⁸
5. Avoids first pass metabolism as it undergoes pre-gastric absorption in buccal, pharyngeal and gastric regions.
6. Provides pleasant feeling in the mouth¹⁷

7. The characteristics of ODTs can simply be adjusted to required levels by reducing or increasing the compression force for each formulation, and/or by only adding formulation aids²⁸
8. A simple direct compression technique is conveniently enough for the preparation of oro-dispersible tablets when suitable excipients are used. Thus conventional manufacturing equipment is sufficient¹⁸
9. Good stability, accurate dosing and easy handling by patients¹⁷
10. Good mechanical properties such as increased hardness and decreased friability¹⁸
11. ODT opened new business opportunity like product differentiation, product promotion, patent extension and life cycle management¹⁷
12. No specific packaging required can be packaged in push through blisters¹⁷
13. They simply vanish when placed in the mouth, so cannot be hidden in mouth by psychotic patients¹⁷

Figure 2 Advantages of ODT

Disadvantages: 17, 18

1. Permeability barrier of the oral mucosa is a disadvantage.
2. Oral absorption surface area is relatively small.
3. Taste masking may be necessary for bitter tasting drugs.
4. Mastication and speech may affect oral absorption of ODT.
5. Decreased volume of saliva may slow the rate of disintegration/dissolution and decrease the bioavailability of the product. Therefore patients with diseases that reduce salivary secretion will not be able to take this formulation.
6. ODT formulations are more susceptible to degradation via temperature and humidity.
7. ODT is hygroscopic in nature so must be kept in dry place.
8. The granules of ODTs sometimes show fragile, effervescence property.

PROPERTIES ESSENTIAL FOR AN ODT PRODUCT:

1. The tablet must possess a disintegration time below 30 s²⁹
2. It should have sufficient strength to withstand the rigors of the manufacturing process and post-manufacturing handling³⁰
3. It should have high drug loading³⁰
4. It should have a pleasant mouth feel³⁰
5. It should be insensitive to environmental conditions such as humidity and temperature³⁰
6. It should be adaptable and amenable to existing processing and packaging machineries³⁰
7. For lyophilized dosage forms, the drug dose must be lower than 400 mg for insoluble drugs and less than 60 mg for soluble drugs³⁰
8. It should leave negligible or no residue in the mouth after oral administration.

MECHANISM OF ODT DISINTEGRATION

Figure 3: Mechanism of ODT disintegration

Figure 4 Mechanism of ODT disintegration

NEED FOR ODT:

1. **Patient factors** - For patients, who find it inconvenient to swallow traditional tablets and capsules like pediatric patients, geriatric patients, patients with fear of choking, patients with persistent nausea, schizophrenic patients, and patients with no access to water³¹⁻³⁴
2. **Effectiveness factors** - For drugs that undergo a great deal of hepatic metabolism. Furthermore, safety profiles may be improved for drugs that produce significant amounts of toxic metabolites mediated by first-pass liver metabolism and gastric metabolism, and for drugs that have a substantial fraction of absorption in the oral cavity and pregastric segments of GIT^{35,36}

3. **Manufacturing and marketing factors** - A new dosage form allows a manufacturer to extend market exclusivity, unique product differentiation, value-added product line extension, and extend patent protection, while offering its patient population a more convenient dosage form. This leads to increased revenue, while also targeting underserved and under-treated patient populations³⁷

EXCIPIENTS USED IN THE FORMULATION OF ODT:

The mixture of excipients used in the formulation of ODT may comprise of at least one disintegrating agent, a soluble diluents, a lubricant and optionally a swelling agent, a permeabilizing agent, sweeteners, flavoring agents and color

The typical property of ODTs can be attained by addition of different varieties of excipients. But the number of fillers/binders/disintegrant which can be used for ODT formulations is limited because these bulk excipients have to fulfill special requirements, such as being soluble in water, pleasant taste, mouth feel, sweetness, and rapid dispersibility. New combinations of existing excipients are an interesting option for improving excipient functionality.

Mannitol is extensively used as diluent but now modified mannitol is available which give extensive flow, compression and rapid dispersibility to the tablet e.g. like Orocell, Mannogem EZ, and Pearlitel SD 200 ¹⁹

Most recently functional excipients also called as co processed excipients are available in market such as Ludiflash, Pharmburst, and F- MELT ¹⁹

Table 4: Composition and characteristics of excipients ¹⁹

Excipients	Composition and characteristics
Pharmburst	Coprocessed blends of Mannitol, Starch, Crosspovidone, Cross Carmellose Sodium, Collidal Silica and Silica
Ludiflash	Coprocessed blends of 90% Mannitol, 5% Kollidon CL-SF (Crosspovidone), 5% Kollicoat SR 30D (Polyvinyl Acetate)
F-MELT	Coprocessed blends of Mannitol, Xylitol, Calcium Sulphate, Crosspovidone, and Mangesium Alumino metasilicate.
Modified chitosan with silicon dioxide	Coprecipitation of Chitosan and Silica.
Orocell 200 & Orocell 400	Orocell 200 with 90% Mannitol (<315µm). Orocell 400 with 90% Mannitol (<500µm).
Advantose	Spray dried disaccharide carbohydrate maltose powder
Polacrillin Potassium	Potassium salt of a cross linked polymer derived from methacrylic acid and divinyl benzene.

Applications:

1. ODT products have been developed for numerous indications ranging from migraines (for which rapid onset of action is important) to mental illness (for which patient compliance is important for treating chronic indications such as depression and schizophrenia.

Challenges:

1. **Proper selection of excipients** for a short disintegration time (less than 3 min – according to the European Pharmacopoeia 6.0, or less than 30 s – recommended by the FDA) ³⁸
2. **Palatability:** As most drugs are unpalatable, the medicaments given as ODTs must be appropriately taste-masked. It is also challenging to the formulators to select the method to be adopted for taste-masking ^{39, 40}
3. **Mechanical strength:** In order to allow ODTs to disintegrate in the oral cavity, they are made of either very porous or soft-molded matrices or compressed into tablets with very low compression force, which makes the tablets friable and/or brittle, difficult to handle. Thus it is challenging to produce ODTs that are sufficiently hard and durable to withstand storage, transportation and handling conditions ⁴¹⁻⁴³
4. **Hygroscopicity:** Several orally disintegrating dosage forms are hygroscopic and cannot maintain physical integrity under normal conditions of temperature and humidity. Hence, they need protection from humidity which calls for specialized product packaging ⁴⁴
5. **Amount of drug:** Only limited amount of drug can be incorporated into a single unit of ODT. Thus it poses a challenge when formulating ODTs for drugs with larger doses.
6. **Aqueous solubility:** Water-soluble drugs pose various formulation challenges because they form eutectic mixtures, which result in freezing-point depression and the formation of a glassy solid that may collapse upon drying because of loss of supporting structure during the sublimation process.

7. To achieve better patient compliance, it is expected that no residue should remain in the mouth, after swallowing.

SELECTION OF DRUGS:

1. Drugs that produce a significant amount of toxic metabolites mediated by first pass liver metabolism and gastric metabolism can be formulated as ODT as it can bypass them by pre-gastric absorption ⁴⁵
2. Drugs that have a substantial fraction of absorption in the oral cavity and segments of the pre-gastric GIT ⁴⁵
3. Drugs having ability to diffuse and partition into the epithelium of the upper GIT (log P > 1, or preferable > 2) and those able to permeate oral mucosal tissue ⁴⁶
4. Drugs with a long half-life and less frequent dosing are mostly preferred ²⁸
5. Drugs which are very bitter or with an unacceptable taste are usually not preferred unless taste masking is possible ²⁸
6. Drugs which require controlled or sustained release are unsuitable candidates of rapidly dissolving oral dosage forms ²⁸
7. Various categories of drugs which require rapid peak plasma concentration like neuroleptics, cardiovascular agents, analgesics, anti-allergic, anti-epileptics, anxiolytics, sedatives, hypnotics, diuretics, anti-parkinsonism agents, anti-bacterial agents and drugs used for erectile dysfunction are suitable ²⁸
8. The drug must have small to moderate molecular weight, good solubility in water and saliva and should be partially unionized at oral cavity pH.

SOME OF THE POTENTIAL DRUG CANDIDATES FOR ODTs: ²⁷

1. **Analgesics and Anti-inflammatory agents:** Aloxiprin, benorylate, difunisal, etodolac, ibuprofen etc.
2. **Anthelmintics:** Albendazole, ivermectin, Dichloropen, cambendazole, mebendazole, etc.

3. **Anti-Arrhythmic agents:** Amiodarone HCl, Disopyramide, Quinidinesulphate.
4. **Anti-bacterial agents:** Cinoxacin, Ciprofloxacin HCl, Clarithromycin, Sulphacetamide, Tetracycline, Trimethoprim, etc
5. **Anti-Coagulants:** Dicoumarol, Dipyridamole, nicoumalone.
6. **Anti-depressants:** Amoxapine, Ciclazindol, Trimipramine maleate.
7. **Anti-diabetics:** Acetohexamide, Chlorpropamide, Glibenclamide, Tolbutamide.
8. **Anti-epileptics:** Beclamide, Carbamazepine, Ethotoin, Methoin, Methsuximide.
9. **Anti-fungal agents:** Amphotericin, Butoconazolenitrate, Clotrimazole, Terbinafine HCl, Terconazole.
10. **Anti-gout agents:** Allopurinol, Probenecid, Sulphinpyrazone.
11. **Anti-hypertensive agents:** Amlodipine, Carvedilol, Benidipine, Prazosin HCl, Reserpine.
12. **Anti-malarials:** Amodiaquine Chloroquine, Mefloquine HCl, Proguanil HCl.
13. **Anti-migraine agents:** Ergotamine tartarate, Pizotifen maleate, Sumatriptan succinate.
14. **Anti-muscarinic agents:** Atropine, Benzhexol HCl, Biperiden, Hyoscine butyl bromide, Orphenadrine.
15. **Anti-neoplastic agents and Immunosuppressants:** Aminoglutethimide, Amsacrine, Busulphan, Etoposide, Mitomycin, Mitozantrone, Testolactone.
16. **Anti-Protazoal agents:** Benznidazole, Decoquinat, Nimotazole, Omidazole.
17. **Anti-thyroid agents:** Carbimazole, Propylthiouracil.
18. **Anxiolytic, Sedatives, Hypnotics and Neuroleptics:** Alprazolam, Amylobarbitone, carbromal, Chlordiazepoxide, Clobazam, Fluanisone, Haloperidol.
19. **Cardiac Inotropic agents:** Amrinone, Digitoxin, Digoxin, Lanatoside C.
20. **Corticosteroids:** Beclomethasone, Betamethasone, Cortosine acetate, Dexamethasone.

Table 5: List of few examples of drugs available as Oro-dispersible tablets (US-FDA approved): ⁴⁷

ACTIVE INGREDIENT	PROPRIETARY NAME	CATEGORY	STRENGTH
Alprazolam	Niravam	Anti-anxiety	0.25mg, 0.5mg, 1mg, 2mg
Amlodipine Besylate	Amlodipine Besylate	Anti-hypertensive	Eq 2.5mg Base, Eq 5mg Base, Eq 10mg Base
Aripiprazole	Abilify	Anti-psychotic	10mg, 15mg, 20mg, 30mg
Baclofen	Kemstro	Muscle relaxant	10mg, 20mg
Cisapride Monohydrate	Propulsid Quicksolv	Gastroprokinetic agent	Eq 20mg Base
Citalopram Hydrobromide	Citalopram Hydrobromide	Central Nervous System Agents - Antidepressant	Eq 10mg Base, Eq 20mg Base, Eq 40mg Base
Clonazepam	Klonopin Rapidly Disintegrating	Antiepileptic	0.125mg, 0.25mg, 0.5mg, 1mg, 2mg
Clozapine	Fazaclo Odt	Central Nervous System Agents - Antipsychotics	50mg
Donepezil Hydrochloride	Aricept Odt	Central Nervous System Agents - Cholinesterase inhibitors	5mg, 10mg
Zolpidem Tartrate	Tovalt Odt	Central Nervous System Agents	5mg, 10mg

TASTE MASKING OF DRUGS IN ODT:

Since most of the APIs are bitter in taste, taste masking is very important and is the first and foremost task in the preparation of ODTs. A number of taste masking techniques are available and are listed below:

- a) Layering the drug onto inert beads using a binder and its subsequent coating with a taste masking polymer ^{48, 49}
- b) Granulating the drug and its subsequent coating with a taste masking polymer ^{49, 50}
- c) Spray-drying the drug dispersed or dissolved in a polymeric solution to get taste-masked particles ^{51, 52}
- d) Complexation by inclusion in cyclodextrin or drug-resinate complex formation ⁵³⁻⁵⁶
- e) Co-acervation to make the drug microencapsulated within a polymer ^{57, 58}
- f) Formation of pellets by extrusion spheronization or mass extrusion ^{59, 60}

TECHNOLOGIES IN THE PREPARATION OF ODT: ⁶¹

- Freeze-Drying or Lyophilization,
- Molding,
- Direct Compression,
- Disintegrant addition,
- Sublimation,
- Spray Drying,
- Mass Extrusion,
- Cotton-candy process,
- NanoCrystal Technology,
- Oral films/ wafers.
- Phase transition process
- Melt granulation.

The orally disintegrating property of these tablets is attributable to the quick ingress of water into the tablet

matrix, which creates porous structure and results in rapid disintegration. Hence, the basic approaches to develop ODTs include maximizing the porous structure of the tablet matrix, incorporating the appropriate disintegrating agent and using highly water-soluble excipients in the formulation.

SPECIFIC EVALUATION TESTS:

1. **Wetting time:** Wetting time of dosage form is related to the contact angle. It needs to be assessed to give an insight into the disintegration properties of the tablets; a lower wetting time implies a quicker disintegration of the tablet. For this purpose, a tablet is placed on a piece of tissue paper folded twice and kept in a small Petri dish (ID = 6.5 cm) containing 6 ml of water, and the time for complete wetting is measured ⁶²
2. **Water absorption ratio:** A small piece of tissue paper folded twice is placed in a small petridish containing 6 ml of water. Put a tablet on the paper and the time required for complete wetting is measured. The wetted tablet is then reweighed. Water absorption ratio, R is determined by using following formula:

$$R = 100 \times (W_a - W_b) / W_b$$

Where, W_b is the weight of tablet before water absorption, W_a is the weight of tablet after water absorption ²²

3. **Taste/ Mouth sensation:** Mouth-feel is critical, and patients should receive a product that feels pleasant. One tablet from each batch is tested for the sensation by placing the tablet on the tongue. The healthy human volunteers are used for evaluation of mouth feel. Taste evaluation is done by a panel of 5 members using time intensity method. Sample equivalent to 40 mg i.e. dose of drug is put in mouth for 10 seconds and record taste instantly and then after 10 secs, 1, 2, 4 and 6 minutes. Volunteer's opinion for the taste is rated by giving different score values i.e. 0 = good, 1 = tasteless, 2 = slightly bitter, 3 = bitter, 4 = awful ²²
4. **Uniformity of dispersion:** Keep the Two tablets in 100ml water and stir gently for 2 minutes. The dispersion is passed through 22 meshes. The tablets will consider passing the test if no residue remained on the screen ²²
5. **Fineness of Dispersion:** This is a qualitative test specified by EP for dispersible tablets. It is an assessment of the grittiness which arises due to disintegration of the tablet into coarse particles. The test is performed by placing two tablets in 100 ml water and stirring it gently, till the tablets get completely disintegrated. The formulation is considered to form a smooth dispersion if the complete dispersion passes through a sieve screen with a nominal mesh aperture of 710 μ m without leaving any residue on the mesh.
6. **Moisture uptake studies:** Moisture uptake studies for ODT should be conducted to have an insight into the stability of the formulation, as several excipients used are hygroscopic. Ten tablets from each formulation are kept in a desiccator over calcium chloride at 37°C for 24 h. The tablets are then weighed and exposed to 75% RH at room temperature for two weeks. The required humidity (75% RH) is achieved by keeping saturated sodium chloride solution at the bottom of the desiccator for three days. One tablet as control (without superdisintegrant) is kept to assess the moisture uptake due to other excipients. Tablets are weighed and the percentage increase in weight is recorded ⁶³

7. **Disintegration time:** The time for disintegration of ODTs is generally less than one minute and actual disintegration time that patient can experience ranges from 5-30 seconds. The USP disintegration apparatus contains six glass tubes that are "3 long, open at the top, and held against 10" screen at the bottom end of the basket rack assembly. One tablet is placed in each tube and the basket rack is poisoned in 1 liter beaker of distilled water at $37 \pm 2^\circ\text{C}$, such that the tablets remain below the surface of the liquid on their upward movement and descend not closer than 2.5cm from the bottom of the beaker ^{22, 64}
8. **Dissolution test:** The dissolution method for ODTs is identical to the approach taken for conventional tablets. Dissolution test was carried out on randomly selected from each formulation using a suitable dissolution apparatus. 1 mL aliquot was withdrawn at given time intervals and the same quantity of samples was immediately replaced with an equal volume of the fresh dissolution medium. Comparative in vitro dissolution study was conducted. The samples were filtered through membrane filters, and analyzed at suitable λ_{max} in a HPLC apparatus. It has been suggested that USP 2 paddle apparatus is the most suitable and common choice for orally disintegrating tablets, with a paddle speed of 50 rpm commonly used ^{65, 66}
9. **Clinical studies:** In vivo studies have been performed on oral fast-disintegrating dosage forms to investigate their behavior in the oral-esophageal tract, their pharmacokinetic and therapeutic efficacy, and acceptability. Its dissolution and buccal clearance was rapid ⁶⁷; the esophageal transit time and stomach emptying time were comparable with those of traditional tablets, capsules, or liquid forms. A decreased inter subject variability in transit time was also observed. ^{68, 69} It also showed good therapeutic efficacy and patient acceptability - particularly in children, ^{70, 71} or when easy administration and rapid onset of action were required (such as for patients undergoing surgery). ^{72, 73} The fast disintegrating forms examined showed improved pharmacokinetic characteristics when compared with reference oral solid formulations. All the drugs that can be absorbed through the buccal and esophageal mucosa exhibited increased bioavailability and side-effect reduction. This is helpful particularly in actives with marked first-pass hepatic metabolism ⁷⁴
10. **Stability studies:** ODT formulations were packed in aluminum foil and exposed to $25 \pm 2^\circ\text{C}/60 \pm 5\%$ relative humidity (RH) and $40 \pm 2^\circ\text{C}/75 \pm 5\%$ RH in stability chambers for 3 months. At pre-set time intervals evaluation of drug content in each tablet was performed ²⁹
11. **Statistical analysis:** The resulting data were analyzed by using SPSS 17.0 software (SPSS Inc., Chicago, USA) applying non-parametric methods. The limit of significance was set at $p < 0.05$ ²⁹

FUTURE OF ODT

Industry observers point to broadening use of ODT technology. These include the incorporation of macromolecules using ODT into vaccines. Other areas include: the incorporation of encapsulated APIs to achieve modified-release profiles within the convenience of an ODT; and the further development of superdisintegrants for incorporation into conventional, compressed tablets,

potentially widening the opportunity for ODT development to non-specialist companies³⁰

Another emerging area is the wider application of 'oral thin-strip technologies'. Thin-film strip technology uses a range of water-soluble polymers and is reported to be able to incorporate water soluble, insoluble, or taste-masked ingredients. The film is manufactured as a continuous sheet and then cut into individual doses prior to packing. The major limitations to this technology are the relatively low doses that can be accommodated (approximately 30 mg) and its moisture sensitivity thus requiring specific unit-dose packaging to protect the product and ensure shelf life⁷⁵

Should next generation drugs be predominantly protein or peptide based, tablets may no longer be the dominant format for dosing such moieties, as ODTs may be more suitable for the oral delivery of these drugs that have limited bioavailability when administered by conventional tablets³⁰

FDC-ODT

There is an ocean of advantage in both FDC products and ODT products. Thus the incorporation of two or more fixed dose combination of drugs into oro-dispersible tablets will have a combined advantage of better compliance and efficacy especially to dysphagic patients.

Definition: "A FDC ODT formulation has a combination of two or more drugs based on scientific and medical rationale in an oro-dispersible tablet form which produces synergistic effect used in treatment of one or even more ailments". This FDC ODT formulation is also expected to give immediate disintegration and therefore rapid drug release thus increasing patient compliance due to their convenience as a dosage form.

Bringing together the techniques of FDC and ODT is desirable because in some cases the disadvantage of one technique can be overcome by the other. For instance, a major disadvantage of the FDC formulations is its size. Combining two or more actives will result in a bigger size of the tablet. But once it is formulated as ODT, the size will not be problem as it will disintegrate in the mouth and there will not be any swallowing issue.

For a successful development of a FDC ODT formulation, bioequivalence comparison between the single and FDC formulations, using in vitro dissolution and Caco-2 apparent permeability (P_{app}) and in silico physiologically based pharmacokinetic modeling approaches should be carried out. Once we come to know that there is no change in bioavailability for FDCs when compared with individual products, we can be sure that the FDC ODT formulations will also be bioequivalent owing to their immediate disintegration and therefore rapid drug release¹⁰

FIXED DOSE COMBINATION OF DRUGS HAVING SCOPE TO BE GIVEN AS ODT PRODUCTS

Research has been carried out using the following combination of drugs

1. Amlodipine + Ramipril⁷⁶
2. Amlodipine + Atorvastatin⁷⁷
3. Ambroxol Hydrochloride + Salbutamol Sulphate⁷⁸
4. Prifinium Bromide + Diclofenac Sodium⁷⁹
5. Ambroxol Hydrochloride + Cetirizine Hydrochloride⁸⁰
6. Lopinavir + Ritonavir⁸¹
7. Hydrochlorothiazide + Amlodipine besylate⁸²

8. Montelukast + Fexofenadine

CONCLUSION

The FDC-ODT products have potential advantages over conventional oral dosage forms as they improved patient compliance; convenience, rapid onset of action and bioavailability which drawn the attention of many manufactures. The patient populations which will be primarily benefited by the FDC-ODT products will be the pediatric and geriatric populations as they will be more prone to swallowing problems and for whom the frequency of dosing has to be reduced. Also these products help to achieve rapid disintegration and instantaneous dissolution of the tablet along with good taste masking properties and excellent mechanical strength. Many drugs can be incorporated in FDC-ODT products, especially unpalatable drugs. In spite of the many advantages it possesses, rarely do the FDC-ODT products come to commercial market. Further research must be carried out properly and more products need to be commercialized to use this technology properly.

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