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Research Article

FAST DISSOLVING TABLET: AN ALTERNATIVE ORAL FORMULATION FOR PAEDIATRIC PATIENTS

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A B S T R A C T

Pediatrics is the branch of medicine dealing with the health and medical care of infants, children, and adolescents from birth up to the age of 18.Paediatrics is different from adult medicine in additional ways than one. The smaller body of an infant or neonate or a toddler is physiologically different from that of an adult. So treating children isn't like treating a miniature adult. Genetic Variance, Congenital defects, and developmental issues are of greater concern to pediatricians than physicians treating adults. Oral routes of drug administration have wide acceptance up to 50-60% of total dosage forms. Solid dosage forms are popular because of ease of administration, accurate dosage, selfmedication, pain avoidance and most importantly the patient compliance. The most popular solid dosage forms are being tablets and capsules; one important drawback of this dosage forms for some patients, is the difficulty to swallow. Drinking water plays an important role in the swallowing of oral dosage forms. In most cases a fast dissolving drug delivery system is a tablet which dissolves or disintegrates in the oral cavity, which can be taken without water or chewing. To mask the taste of the active ingredient substances must be included in 90% of fast dissolving delivery system. The masked active ingredient is swallowed by patient's saliva along with the soluble and insoluble ingredients. Others are also known as melt-in-mouth tablets, reprimelts, porous tablets, orodispersible, quick dissolving or rapid disintegrating tablets. Fast dissolving tablets are also called as mouth-dissolving tablets, melt-in mouth tablets, Orodispersible tablets, rapimelts, porous tablets, quick dissolving etc. Fast dissolving tablets are those when put on tongue disintegrate instantaneously releasing the drug which dissolve or disperses in the saliva. Their growing importance was underlined recently when European pharmacopoeia adopted the term "Orodispersibletablet" as a tablet which should disperse/disintegrate in less than three minutes. The bioavailability of some drugs may be increased due to absorption of drug in oral cavity and also due to pregastric absorption of saliva containing dispersed drugs that pass down into the stomach. The technologies used for manufacturing fast-dissolving tablets are freeze-drying, spray-drying, tablet molding, sublimation, sugar-based excipients, tablet compression, and disintegration addition.

INTRODUCTION

Pharmacotherapy in children requires medicinal products in age-appropriate dosage forms and flexible dose strengths. Healthcare professionals often encounter a lack of licensed and commercially available formulations, which results in the need for manipulation. This study aimed to investigate the nature, frequency and preventability of the manipulation of medicinal products before oral drug administration to paediatric inpatients in Germany. A prospective, direct observational approach was used. Two thousand and three medication preparation processes (MPP) in 193 patients were included in the analysis. Medicines were manipulated in 37% of oral administrations, affecting 57% of the patients. The percentage of manipulations was highest in infants/toddlers (42%) and lowest in adolescents (31%). Antiepileptics were most frequently manipulated (27%), followed by vitamins (20%) and drugs for acid-related disorders (13%). Fifty-six per cent of all manipulations were off-label. In 71% of these, no alternative appropriate medicinal product was commercially available. These results demonstrate that the manipulation of medicinal products before oral administration is common in paediatric wards in Germany. About half of the manipulations were off-label, indicating that no suitable formulation was available. Evidence-based guidelines for manipulations are required, with the overall aim of improving the safety of paediatric drug therapy.

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Recent changes in medical education have highlighted the importance of experiential learning. Simulation is one model that has gained significant attention in the last decade and has been widely adopted as a training and assessment tool in medical education. Paediatric simulation has been utilized to teach various skills including resuscitation and trauma management, procedural skills and team training. It is also a valuable tool for health care educators, as it allows learners to achieve competence without putting patients at risk. Recent literature demonstrates increased retention of knowledge and skills after simulation based training. Further research is required to improve current simulation curriculums, develop validated assessment tools and to demonstrate improved clinical outcomes after simulation based training. We conducted an online search of original and review articles related to simulation and paediatric medical education and provide an overview of the role and utility of simulation in paediatrics.

All physicians face the challenge of keeping abreast with a body of medical knowledge that is growing at an exponential rate. On this account, physicians often spend countless hours each month reading journals to "keep current" with recently described techniques of diagnosis and therapy. To gain maximal benefit from their reading, physicians must be able to assess the scientific merit of published research. They must evaluate the various claims and conclusions and then decide which are valid and applicable to their own clinic settings. This type of critical insight requires familiarity with basic principles of good study design and with biostatistical logic and procedures.

Unfortunately, recent studies have demonstrated that physicians9 concepts regarding statistics are often inaccurate, and even more disturbing, that readers are often willing to draw conclusions unsupported by the available data. Some authorities have therefore recommended remedial statistical training for physicians by means of increased attention to statistical issues in biomedical journals. The question of exactly which statistical concepts and techniques need to be mastered, however, remains largely unanswered.

Pediatric aspects are nowadays integrated early in the development process of a new drug. The stronger enforcement to obtain pediatric information by the regulatory agencies in recent years resulted in an increased number of trials in children. Specific guidelines and requirements from, in particular, the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) form the regulatory framework. This review summarizes the regulatory requirements and strategies for pediatric drug development from an industry perspective. It covers pediatric study planning and conduct, considerations for first dose in children, appropriate sampling strategies, and different methods for data generation and analysis to generate knowledge about the pharmacokinetics (PK) and pharmacodynamics (PD) of a drug in children. The role of Modeling and Simulation (M&S) in pediatrics is highlighted including the regulatory basis-and examples of the use of M&S are illustrated to support pediatric drug development.

Drug delivery system is an efficient tool for enhancing market, extending product life cycles and creating opportunities.DDS makes a significant contribution to global pharmaceutical sales through market segmentation, and are moving rapidly. Fast Dissolving Drug Delivery Systems(FDDTs) can be achieved by various conventional methods like direct compression, wet granulation, moulding, spray drying, freeze drying, sublimation. Fast disintegrating tabletsare made of either very porous and soft molded matrices or compressed into tablets with very low compression force in order to allow FDTs to dissolve in the mouth. Tablets and capsules are the most popular dosage forms.

We conducted a feasibility study to develop a formulation for these drugs with child-safe excipients in a flexible dosage form for children across the pediatric age spectrum. The freeze-drying-in-blister approach was used to produce fast-dissolving tablets (FDTs), as these can be dispersed in fluids for easy administration, even to infants, and appropriate portions of the dispersion can be given for different ages/weights. We combined various ratios of polymers, surfactants, and bulking agents to an incorporate the two highly hydrophobic drugs while maintaining drug stability, rapid disintegration, and good handling properties.

Paediatric dosage forms

Paediatric dosage forms should be versatile so that drugs can be administered to neonates, children, and adolescents. The common paediatric dosage forms include solid dosage forms (such as tablets); powders, solutions, and syrups (Viner and Barker, 2005). Solid dosage forms are drugs, which have been compounded to give a definite shape and a standard dose, as is the case with tablets. Powders are a type of solid dosage form, which have been ground and are finely divided. They are usually administered topically on the skin, sprinkled on food or mixed with liquid diet. On the other hand, solutions are dosage forms which are made up of an aqueous base (majority) and other pharmaceutical ingredients which give the solution its therapeutic effect. Syrups form sugary and have a thicker consistency than solutions, a factor which makes them more viscous (Ansel *et al*.,) [1-5].

Age development and dosage forms of choice

Dealing with children is quite challenging, particularly when it comes to diseases and their remedies. For neonates, the challenge is even more pronounced because diagnosis alone poses a difficult step. After diagnosis, other challenges include the appropriate choice of formulation and route of administration. Children are remarkably sensitive to the effects of drugs; not just on the internal effects that the drugs have but also on the outward appearance and the taste. A child may refuse to take a drug because the color is not appealing or because it smells 'weird'. Even after succeeding in making the child swallow the drug in the first instance, this result may not be repeated for subsequent doses. This is because children have a unique fine memory to conditions, circumstances, and experiences of their past (Sahler *et al*.,). To say the least, it will pose a massive challenge trying to convince them to take the drug again.

For this reason, paediatric dosage forms need to be tailored to address the fears and the expectations of the target users. This request for a higher level of interest during manufacturing and even prescribing, since children require lower dose amounts to achieve the same effects as seen in adults. In addition, various factors need to be taken into consideration, notably taste

masking. For drugs that come in the form of powders, the dosage form can be changed by tableting the powders and converting them into solid dosage forms. Powders can also be granulated to make it easier to determine the dose since this becomes a major issue, especially with regard to children (van Riet-Nales *et al*.,). Table shows a matrix developed by the EMA from responses to questionnaires sent out to 40 participants (including parents, pharmaceutical scientists and clinical pediatricians) in different European countries to develop a relationship between age development, dosage form and route of administration (Cram *et al*.,). Moving from the left to the right, the emphasis in the columns changes from the applicability to preference[6].

Draft EMA guidance proposed that, 'small tablets (i.e. tablets from 3 to 5 mm diameter, width or length whichever is the longest) will not be considered acceptable for children below the age of 2 years, medium sized tablets (i.e. tablets from 5 to 10 mm) for children below the age 6 years, large tablets (i.e. tablets from 10 to 15 mm) for children below the age of 12 years and very large tablets (i.e. tablets from 15 mm) for children below the age of 18 years' [11],however, this recommendation was removed from the updated guidance document [12] Studies that investigated the use of mini-tablets (tablets ≤3 mm) found that mini-tablets were a potential dosage form suitable for 2–6 year old (based on placebo tablets 3 mm in diameter)[13]

Table 1 EMA matrix relating oral dosage forms/ route of administration to dosage form and age; adapted from references (EMA, 2006, Breitkreutz and Boos, 2007)[7,8]

Oral dosage forms	Preterm new-born infants	Term new-born infants (0 d-28 d)	Infants and Toddlers (1 m-2 y)	Children (pre-school) (2-5 y)	Children (school) (6-11 y)	Adolescents (12-16/18 y)
Solutions/ drops	2	4	5	5	4	4
Emulsion/Suspension	2	3	4	5	4	4
Effervescent dosage form	2	4	5	5	4	4
Powders/Multiparticulates	1	2	2	4	4	5
Tablets	1	1	1	3	4	5
Capsules	1	1	1	2	4	5
Orodispersible dosage form	1	2	3	4	5	5
Chewable tablets	1	1	1	3	5	5

Solids for reconstitution

The use of dispersible tablets, powders, granules, pellets or sprinkles for reconstitution is a popular strategy in paediatric formulation development as the solid product typically has better stability compared with a formulated liquid. However, these reconstituted products also need to be taste-masked. Reconstitution can occur either at the point of dispensing or at the point of administration depending on the product. The instructions for reconstitution can be complicated for untrained individuals, yet it is important that the final product contains the correct dosage for the patient. If these solids for reconstitution are administered in the absence of water they are only appropriate for infants who are accepting solid food (typically >6 months). For solids of a larger particle size the minimum age range may be higher owing to the risk of aspiration or choking.

If dispersible products are not reconstituted in an appropriate volume of liquid then there is a risk of local tissue injury (similar to when tablets adhere to the esophagus [9] and a delay in the onset of action, since the solid material needs to dissolve prior to absorption. Therefore, it is important to consider the overall solubility of any drug and how this may affect biopharmaceutical performance.

The volume of liquid used for administration of dispersible tablets is larger (up to 20 ml) than volumes typically used for conventional oral liquids, with volumes up to 20 ml considered (by the EMA) to be appropriate for children below the age of 4 years and volumes of 50 ml for those over 4 years old.

Oral solid dosage forms – conventional tablets and capsules

Conventional tablets are limited by their rigid dose content and the ability of the child to swallow a tablet. The general thinking is that children will accept tablets based on size, where a smaller tablet is more likely to be acceptable. Tablets can be scored to allow splitting to reduce their size yet this can result in inaccurate dosages within the fragmented tablets [10].

Additionally Spomer and co-workers found that very young children (6–12 months) were fully capable of swallowing mini-tablets of 2 mm diameter, often accepting them in preference to sweet liquid formulations.[14]

Standardized capsule sizes range from 11.1 mm (size 5) to 23.3 mm (size 00) in length. There are no data on acceptability of capsule size in children although this should be considered to be equivalent to tablets. Capsules can be opened and the contents taken to improve acceptability in children. However this should only be undertaken when justified. However, the capsule contents may taste unpleasant and the bioavailability of the opened capsule may differ from that of the intact product.

In adults the recommended volume of water taken with tablets and capsules is 250 ml based on clinical study protocol used during development of such products [15] The use of smaller volumes can delay onset of absorption and reduce the overall bioavailability of a product, particularly drugs that are poorly water soluble [16,17] There are no literature reports that provide a similar volume of water to be used in children. Therefore water ingestion may increase the variability in exposure observed following tablet administration in children.

Chewable tablets and orodispersible formulation

Chewable tablets and orodispersible formulations need to possess good organoleptic properties including a good mouth feel which is influenced by the drug's crystalline structure and solubility. The consequences of swallowing such tablets whole should be considered and it is preferable that their bioavailability is unaffected. WHO guidance suggests that they should be developed such that the label can state, 'tablets that may be chewed or swallowed whole'.[18]

Orodispersible tablets, oral lyophilisates and oral films are solid products that are designed to dissolve within the oral cavity. These products dissolve and disperse within the saliva

for absorption either directly from the oral cavity or for absorption from the gastrointestinal tract following ingestion. The ratio of absorption from each of these sites can be important, particularly for drugs that show differences in bioavailability from each route, for example desmopressin.[19] These products offer the level of pharmaceutical stability associated with solid dosage forms and are acceptable to even very young patients. However, they are limited by dose rigidity in the same way as conventional tablets. They are most suited to highly soluble drugs, although the solubility of the drug needs to be balanced with taste-masking as highly soluble drugs will activate taste receptors on the tongue if they dissolve in saliva within the oral cavity.[20]

The volume of liquid taken with such products should also be considered, particularly for poorly water soluble drugs as described previously.

Oral liquids

The bitter taste associated with many drugs is thought to have evolved as a deterrent against ingesting toxic substances.[21] The major barrier in development of oral liquid formulations is taste-masking of drugs as more than 90% of paediatricians in the US reported that a drug's taste and palatability were the greatest barriers to completing treatment.[22] In some cases simple taste-masking is insufficient and more complex formulations are required to encapsulate the drug providing taste-concealing properties. The excipients used in the development of a product need to be safe and acceptable for use in children. Excipients are typically used to optimize the formulation of the medicine to improve palatability, shelf-life and/or manufacturing processes. There are certain excipients that should not be used in children's' medicines as they can retard on-going organ development, for example, ethanol, propylene glycol, benzyl alcohol and parabens .[23] It is also important to consider the electrolyte concentration when developing medicines for neonates where renal function may be immature.

The maximum recommended single dosing volume is 5 ml for children aged below 4 years and 10 ml for children aged between 4 and 12 years according to EMA draft guidance.[24] Oral liquid drops provide a mechanism to deliver small volumes or low doses of a drug to children and are particularly useful in very young children. The use of appropriate measuring devices with oral medicines is encouraged, particularly the use of oral syringes as they have superior accuracy compared with graduated pipettes or measuring spoons.[25]

Liquids provide maximal dosing flexibility and it is possible to use a single formulation over a wide age range (including neonates). However the volume used must be acceptable to the patient and the dosing device must be fit for purpose.

Fast Dissolving Tablet

Introduction

Oral routes of drug administration have wide acceptance up to 50-60% of total dosage forms. Solid dosage forms are popular because of ease of administration, accurate dosage, selfmedication, pain avoidance and most importantly the patient compliance. The most popular solid dosage forms are being tablets and capsules; one important drawback of this dosage forms for some patients, is the difficulty to swallow. Drinking water plays an important role in the swallowing of oral dosage forms. Often times people experience inconvenience in swallowing conventional dosage forms such as tablet when water is not available, in the case of the motion sickness (kinetosis) and sudden episodes of coughing during the common cold, allergic condition and bronchitis.[26]

In most cases a fast dissolving drug delivery system is a tablet which dissolves or disintegrates in the oral cavity, which can be taken without water or chewing. To mask the taste of the active ingredient substances must be included in 90% of fast dissolving delivery system. The masked active ingredient is swallowed by patient's saliva along with the soluble and insoluble ingredients. Others are also known as melt-in-mouth tablets, reprimelts, porous tablets, orodispersible, quick dissolving or rapid disintegrating tablets.

Fast dissolving tablets are also called as mouth-dissolving tablets, melt-in mouth tablets, Orodispersible tablets, rapimelts, porous tablets, quick dissolving etc. Fast dissolving tablets are those when put on tongue disintegrate instantaneously releasing the drug which dissolve or disperses in the saliva. The faster the drug into solution, quicker the absorption and onset of clinical effect. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablets dosage form.[27]

Their growing importance was underlined recently when European pharmacopoeia adopted the term "Orodispersible tablet" as a tablet that to be placed in the mouth where it disperses rapidly before swallowing. According to European pharmacopoeia, the ODT should disperse/disintegrate in less than three minutes. The basic approach in development of FDT is the use of superdisintegrants like cross linked carboxymethyl cellulose (croscarmellose), sodium starch glycolate (primogel, explotab), polyvinylpyrollidone (polyplasdone) etc, which provide instantaneous disintegration of tablet after putting on tongue, their by release the drug in saliva.

The bioavailability of some drugs may be increased due to absorption of drug in oral cavity and also due to pregastric absorption of saliva containing dispersed drugs that pass down into the stomach. More ever, the amount of drug that is subjected to first pass metabolism is reduced as compared to standard tablet. The technologies used for manufacturing fast-dissolving tablets are freeze-drying, spray-drying, tablet molding, sublimation, sugar-based excipients, tablet compression, and disintegration addition.As a result of increased life expectancy, the elderly constitute a large portion of the worldwide population today. These people eventually will experience deterioration of their physiological and physical abilities.[28]

Criteria for Fast dissolving Drug Delivery System

The tablets should

- Not require water to swallow, but it should dissolve or disintegrate in the mouth in matter of seconds.
- Be compatible with taste masking.
- Be portable without fragility concern.

- Have a pleasant mouth feel. Leave minimum or no residue in the mouth after oral administration.
- Exhibit low sensitive to environmental condition as temperature and humidity.
- Allow the manufacture of the tablet using conventional processing and packaging equipment's at low cost.

Salient Feature of Fast Dissolving Drug Delivery System

- Ease of Administration to the patient who can not swallow, such as the elderly, stroke victims, bedridden patients, patient affected by renal failure and patient who refuse to swallow such as pediatric, geriatric & psychiatric patients.
- No need of water to swallow the dosage form, which is highly convenient feature for patients who are traveling and do not have immediate access to water.
- Rapid dissolution and absorption of the drug, which will produce quick onset of action.
- Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach. In such cases bioavailability of drug is increased.
- Pregastric absorption can result in improved bioavailability and as a result of reduced dosage; improve clinical performance through a reduction of unwanted effects.
- Good mouth feel property helps to change the perception of medication as bitter pill particularly in pediatric patient.
- The risk of chocking or suffocation during oral administration of conventional formulation due to physical obstruction is avoided, thus providing improved safety.
- New business opportunity like product differentiation, product promotion, patent extensions and life cycle management.
- Beneficial in cases such as motion sickness, sudden episodes of allergic attack or coughing, where an ultra rapid on set of action required.
- An increased bioavailability, particularly in cases of insoluble and hydrophobic drugs, due to rapid disintegration and dissolution of these tablets.
- Stability for longer duration of time, since the drug remains in solid dosage form till it is consumed. So, it combines advantage of solid dosage form in terms of stability and liquid dosage form in terms of bioavailability.

Advantages of fast dissolving tablets

- There is no requirement of water for the swallowing of tablets.
- This can be administrated easily for pediatric, elderly and mentally disabled patients.
- When compared to liquids, this gives correct dosing.
- Quick on set of action is offered which is due to rapid dissolution and absorption.
- There is an increase in the bioavailability of drugs.
- When compared to liquid medication it is advantages in specification to administration and also transportation.
- There is a reduction of first pass metabolism which offers improvement in bioavailability and so there is a decrease in the dose.
- There is a gratuitous exposure of suffocation which is caused due to physical obstruction when swallowed.
- It grant loading of high drug.
- Administered without water, anywhere, any time.
- Suitability for geriatric and pediatric patients, who experience difficulties in swallowing and for the other groups that may experience problems using conventional oral dosage form, due to being mentally ill, the developmentally disable and the patients who are un-cooperative, or are on reduced liquid intake plans or are nauseated.
- Beneficial in cases such as motion sickness, suede episodes of allergic attack or coughing, where an ultra rapid on set of action required.
- An increased bioavailability, particularly in cases of insoluble and hydrophobic drugs, due to rapid disintegration and dissolution of these tablets.
- Stability for longer duration of time, since the drug remains in solid dosage form till it is consumed. So, it combines advantage of solid dosage form in terms of stability and liquid dosage form in terms of bioavailability.

Disadvantages

- Fast dissolving tablets must be kept in dry place as it they are hygroscopic in nature.
- If maintains the mouth feeling periodically.
- For proper stabilization & safety fast dissolving tablets require special package.
- Careful handling of the tablet is required as the tablet consistently have insufficient mechanical strength.
- If the tablets formulation is not preformed properly, the tablets may leave unpleasant taste or grittiness in the mouth.
- The tablets usually have insufficient mechanical strength. Hence, careful handling is required.
- The tablets may leave unpleasant taste and/or grittiness in mouth if not formulated properly.

Objection in formulation fast dissolving tablets:[29]

Palatability

Fast Dissolving Tablets are generally taste mask the drug form 90% of the drugs are unpalatable it when they disintegrate or dissolve in patient's oral cavity on administration the drug, comes in contact with taste buds, so masking of the taste of the drugs becomes derogatory to patient amenability.

Mechanical strength

Fast dissolving tablets are made of either permeable and soft molded matrices or pressed into tablets with decreased compression force which causes the tables friable or brittle, difficulty in handling and generally requires specialized peel of blister packing which causes increase in the cost. These are done in order to allow Fast Dissolving Tablets to disintegrate in the oral cavity.

Amount of drug

The technologies applied which are used for Fast Dissolving Tablets are narrowed by the amount of drugs which can be incorporated into each unit dose. The dose of the drug for insoluble drugs and soluble drugs are respectively less than

400 mg and being for lyophilized dosage forms.This guideline particularly challenges during the formulation of fast dissolving oral films or wafers. Aqueous formulation challenges are presented by water soluble drugs as they form eutectic mixtures which develops in freezing point depression and a glassy solid is formed which collapse on drying during sublimation process due to the loss of supporting structure. These collapses can be intereputed sometimes with the help of diverse matrix forming excipients like mannitol which induces crystallinity and thus transmit rigidity to the amorphous composite.

Size of tablets: [30]

The comfort of tablets administration depends on its size. For swallowing uncomplicated size of the tablets is 7-8mm where as the accessible size to handle was the one which is larger than 8mm has been reported.

Techniques for Preparing Fast dissolving Tablets

Many techniques have been reported for the formulation of Fast dissolving tablets or Orodispersible tablets.[31,32,33,34]

1. Freeze drying / lyophilization
2. Tablet Moulding
3. Spray drying
4. Sublimation
5. Direct compression
6. Mass extrusion
7. Disintegrates addition

Freeze-Drying or Lyophilization

Freeze drying is the process in which water is sublimed from the product after it is frozen. This technique creates an amorphous porous structure that can dissolve rapidly. A typical procedure involved in the manufacturing of ODT using this technique is mentioned here. The active drug is dissolved or dispersed in an aqueous solution of a carrier/polymer. The mixture is done by weight and poured in the walls of the preformed blister packs. The trays holding the blister packs are passed through liquid nitrogen freezing tunnel to freeze the drug solution or dispersion. Then the frozen blister packs are placed in refrigerated cabinets to continue the freeze-drying. After freeze-drying the aluminum foil backing is applied on a blister-sealing machine. Finally the blisters are packaged and shipped. The freeze-drying technique has demonstrated improved absorption and increase in bioavailability. The major disadvantages of lyophillization technique are that it is expensive and time consuming; fragility makes conventional packaging unsuitable for these products and poor stability under stressed conditions.

Tablet Molding

Molding process is of two types i.e. solvent method and heat method. Solvent method involves moistening the powder blend with a hydro alcoholic solvent followed by compression at low pressures in molded plates to form a wetted mass (compression molding). The solvent is then removed by air-drying. The tablets manufactured in this manner are less compact than compressed tablets and posses a porous structure that hastens dissolution. The heat molding process involves preparation of a suspension that contains a drug, agar and sugar (e.g. mannitol or lactose) and pouring the suspension in the blister packaging wells, solidifying the agar at the room temperature to form a jelly and drying at 30○C under vacuum. The mechanical strength of molded tablets is a matter of great concern. Binding agents, which increase the mechanical strength of the tablets, need to be incorporated. Taste masking is an added problem to this technology.

The taste masked drug particles were prepared by spray congealing a molten mixture of hydrogenated cottonseed oil, sodium carbonate, lecithin, polyethylene glycol and an active ingredient into a lactose based tablet triturate form. Compared to the lyophillization technique, tablets produced by the molding technique are easier to scale up for industrial manufacture.

Spray Drying

In this technique, gelatin can be used as a supporting agent and as a matrix, mannitol as a bulking agent and sodium starch glycolate or crosscarmellose or crospovidone are used as superdisintegrants. Tablets manufactured from the spray-dried powder have been reported to disintegrate in less than 20 seconds in aqueous medium. The formulation contained bulking agent like mannitol and lactose, a super disintegrant like sodium starch glycolate & croscarmellose sodium and acidic ingredient (citric acid) and/or alkaline ingredients (e.g. sodium bicarbonate). This spray-dried powder, which compressed into tablets showed rapid disintegration and enhanced dissolution.

Sublimation

To generate a porous matrix, volatile ingredients are incorporated in the formulation that is later subjected to a process of sublimation. Highly volatile ingredients like ammonium bicarbonate, ammonium carbonate, benzoic acid, camphor, naphthalene, urea, urethane and phthalic anhydride may be compressed along with other excipients into a tablet. This volatile material is then removed by sublimation leaving behind a highly porous matrix. Tablets manufactured by this technique have reported to usually disintegrate in 10-20 sec. Even solvents like cyclohexane; benzene can be used as pore forming agents.

Direct Compression

For the manufacturing of tablets, this is the easiest way. In direct compression, conventional equipment ,commonly available excipients and a limited no. of processing steps are involved. High doses can be domiciled and concluded weight of the tablet can easily outpace than other production methods. Solubilization and disintegration of directly compressed tablets depends on single/combined action of disintegrate, excipients which are water soluble and effervescent agent.

Superdisintegrants

In many orally disintegrating tablet technologies based on direct compression, the addition of superdisintegrants principally affects the rate of disintegration and hence the dissolution. The presence of other formulation ingredients such as water-soluble excipients and effervescent agents further hastens the process of disintegration.

Sugar Based Excipients

This is another approach to manufacture ODT by direct compression. The use of sugar based excipients especially bulking agents like dextrose, fructose, isomalt, lactilol, maltilol, maltose, mannitol, sorbitol, starch hydrolysate, polydextrose and xylitol, which display high aqueous solubility and sweetness, and hence impart taste masking property and a pleasing mouthfeel. Mizumito *et al* have classified sugar-based excipients into two types on the basis of molding and dissolution rate.

Type 1 saccharides (lactose and mannitol) exhibit low mouldability but high dissolution rate. Type 2 saccharides (maltose and maltilol) exhibit high mouldability and low dissolution rate.

Mass-Extrusion

This technology involves softening the active blend using the solvent mixture of water-soluble polyethylene glycol and methanol and subsequent expulsion of softened mass through the extruder or syringe to get a cylinder of the product into even segments using heated blade to form tablet. The dried cylinder can also be used to coat granules for bitter drugs and thereby achieve taste masking.

Disintigrates addition

For the formulation of fast dissolving tablets disintegrates additional technique is one of the most prominent techniques as its implementation is easy and cost effectiveness.

Important Patented Technologies for Fast Dissolving Tablets

ZydisTechnology

Zydis formulation is a unique freeze dried tablet in which drug is physically entrapped or dissolved within the matrix of fast dissolving carrier material. When zydis units are put into the mouth, the freeze-dried structure disintegrates instantaneously and does not require water to aid swallowing. The zydis matrix is composed of many material designed to achieve a number of objectives. To impart strength and resilience during handling, polymers such as gelatin, dextran or alginates are incorporated. These form a glossy amorphous structure, which imparts strength.

To obtain crystallinity, elegance and hardness, saccharides such as mannitol or sorbitol are incorporated. Water is used in the manufacturing process to ensure production of porous units to achieve rapid disintegration while various gums are used to prevent sedimentation of dispersed drug particles in the manufacturing process. Collapse protectants such as glycine prevent the shrinkage of zydis units during freeze-drying process or long-term storage. Zydis products are packed in blister packs to protect the formulation from moisture in the environment.

Durasolv Technology

Durasolv is the patented technology of CIMA labs. The tablets made by this technology consist of drug, filler and a lubricant. Tablets are prepared by using conventional tableting equipment and have good rigidity. These can be packaged into conventional packaging system like blisters. Durasolv is an appropriate technology for product requiring low amounts of active ingredients.

Orasolv Technology

CIMA labs have developed Orasolv Technology. In this system active medicament is taste masked. It also contains effervescent disintegrating agent. Tablets are made by direct compression technique at low compression force in order to minimize oral dissolution time. Conventional blenders and tablet machine is used to produce the tablets. The tablets produced are soft and friable.

Flash Dose Technology

Flash dose technology has been patented by fuisz. Nurofen melt let, a new form of ibuprofen as melt in mouth tablets prepared using flash dose technology is the first commercial product launched by biovail corporation. Flash dose tablets consist of self-binding shear form matrix termed as “floss”. Shear form matrices are prepared by flash heat processing.

Wow tab Technology

Wow tab technology is patented by Yamanouchi Pharmaceutical Co. WOW means “Without Water”. In this process, combination of low mouldability saccharides and high mouldability saccharides is used to obtain a rapidly melting strong tablet. The active ingredient is mixed with a low mouldability saccharide (eg. lactose, glucose, and mannitol) and granulated with a high mouldability saccharide (eg. Maltose, oligosaccharides) and compressed into table.

Flash tab Technology

Prographarm laboratories have patented the Flash tab technology. Tablet prepared by this system consists of an active ingredient in the form of micro crystals. Drug micro granules may be prepared by using the conventional techniques like coacervation, micro encapsulation and extrusion spheronisation. All the processing utilized conventional tableting technology.

Table 2 List of commercially Available Fast dissolving tablets

Trade Name	Active Drug	Manufacturer
Felden fast melt	Piroxicam	Pfiser Inc., NY, USA
Claritin redi Tab	Loratidine	Schering plough Corp., USA
Maxalt MLT	Rizatriptan	Merck and Co., NJ, USA
Zyprexia	Olanzapine	Eli lilly, Indianapolis, USA
Pepcid RPD	Famotidine	Merck and Co., NJ, USA
Zofran ODT	Ondansetron	Glaxo Wellcome, Middlesex, UK
Zoming-ZMT	Zolmitriptan	AstraZeneca, Wilmington, USA
Zeplar TM	Selegilline	Amarin Corp., London, UK
TempraQuiclets	Acetaminophen	Bristol myers Squibb, NY, USA
Febrectol	Paracetamol	Prographarm, Chateauneuf, France
Nimulid MDT	Nimesulide	Panacea Biotech, New delhi, India
Torrox MT	Rofecoxib	Torrent pharmaceuticals, India
Olanexinstab	Olanzapine	Ranbaxy lab. Ltd. New-delhi, India
Romilast	Montelukast	Ranbaxy lab. Ltd. New-delhi, India
Benadryl Fastmelt	Diphenhydramine and pseudoephedrine	Warner Lambert, NY, USA

Mechanism of Superdisintegrants

There are four major mechanisms for tablets disintegration as follows[35]

Swelling

Perhaps the most widely accepted general mechanism of action for tablet disintegration is swelling. Tablets with high porosity

show poor disintegration due to lack of adequate swelling force. On the other hand, sufficient swelling force is exerted in the tablet with low porosity. It is worthwhile to note that if the packing fraction is very high, fluid is unable to penetrate in the tablet and disintegration is again slows down.

Porosity and capillary action (Wicking)

Disintegration by capillary action is always the first step. When we put the tablet into suitable aqueous medium, the medium penetrates into the tablet and replaces the air adsorbed on the particles, which weakens the intermolecular bond and breaks the tablet into fine particles. Water uptake by tablet depends upon hydrophilicity of the drug /excipient and on tableting conditions. For these types of disintegrants maintenance of porous structure and low interfacial tensiontowards aqueous fluid is necessary which helps in disintegration by creating a hydrophilic network around the drug particles.

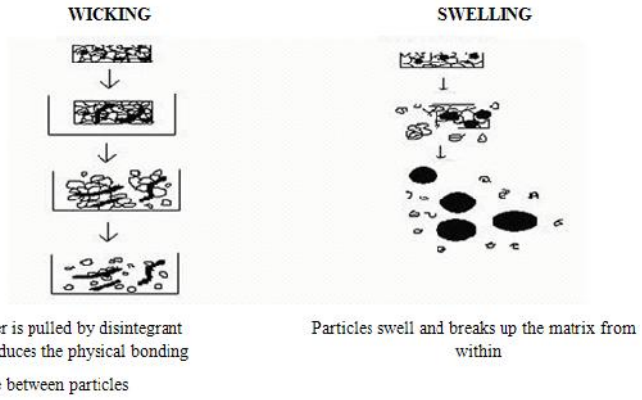

Figure 1

Due to disintegrating particle/particle repulsive forces

Another mechanism of disintegrated attempts to explain the swelling of tablet made with 'non-swellable' disintegrants. Guyot-Hermann has proposed a particle repulsion theory based on the observation that nonswelling particle also cause disintegration of tablets. The electric repulsive forces between particles are the mechanism of disintegration and water is required for it. Researchers found that repulsion is secondary to wicking.

Due to deformation

During tablet compression, disintegranted particles get deformed and these deformed particles get into their normal structure when they come in contact with aqueous media or water.

Occasionally, the swelling capacity of starch was improved when granules were extensively deformed during compression. This increase in size of the deformed particles produces a break up of the tablet. This may be a mechanism of starch and has only recently begun to be studied.

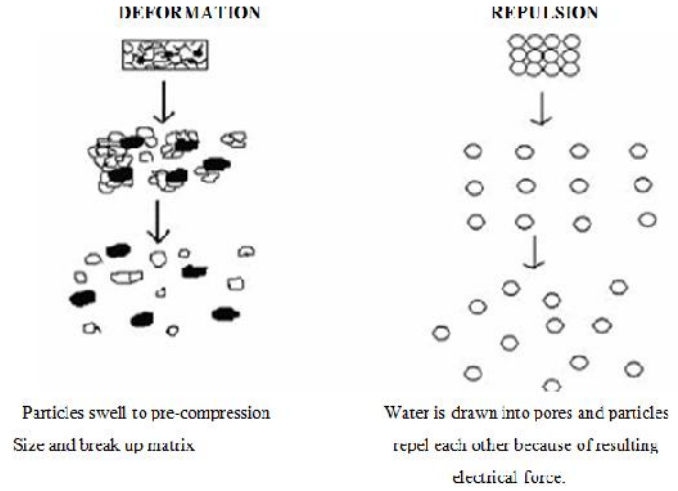

Figure 2

Preformulation studies fast dissolving tablet

Preformulation study relates to pharmaceutical and analytical investigation carried out proceeding and supporting formulation development efforts of the dosage form of the drug substance. Preformulation yields basic knowledge necessary to develop suitable formulation for the toxicological use. It gives information needed to define the nature of the drug substance and provide frame work for the drug combination with pharmaceutical excipients in the dosage form. Hence, the following preformulation studies were performed on the obtained sample of drug.

CONCLUSION

Fast dissolving tablets are novel approach in market having property to enhance the release of drugs within 5-15 minutes. Fast dissolving tablets have advantage over conventional tablets and liquid dosage. Due to case of administration, they are first preference of doctors for patients of any age group .We can conclude that fast dissolving tablets can be used safely and effectively over conventional tablets.

Paediatric formulations need to be appropriate for the child in terms of dose, convenience and acceptability to ensure compliance with the medication.

Table 3 List of super disintegrants

Superdisintegrants	Example	Mechanism Of action	Special comment
Crosscarmellose® Ac-Di-Sol® Nymce ZSX® Primellose® Solutab® Vivasol® L-HPC	Crosslinked cellulose	-Swells 4-8 folds in < 10 seconds. -Swelling and wicking both.	-Swells in two dimensions. -Direct compression or granulation -Starch free
CrosspovidoneCrosspovidon M® Kollidon® Polyplasdone®	Crosslinked PVP	-Swells very little andreturns to original size aftercompression but act by capillary action	-Water insoluble and spongy in nature so get porous tablet
Sodium starch glycolate Explotab® Primogel®	Crosslinked starch	-Swells 7-12 folds- in < 30 seconds	-Swells in three dimensions and high level serve as sustain release matrix
Alginic acid NF Satialgine®	Crosslinked alginic acid	-Rapid swelling in aqueous medium or wicking action	-Promote disintegration in both dry or wet granulation
Soy polysaccharides Emcosoy®	Natural super disintegrant		-Does not contain any starch or sugar. Used in nutritionalproducts.
Calcium silicate		-Wicking action	Highlyporous, Optimum concentration is between 20-40%

There are differences in paediatric anatomy and physiology that can impact upon the performance of a drug that is different from that observed in adults. The design of a paediatric formulation needs to take these differences in physiology into account to ensure that the pharmacokinetic profile of the drug is not compromised. This is of particular relevance to neonates and infants who are furthest in development terms from an adult.

Formulation can lead to differences in pharmacokinetic profiles for a drug, highlighting the risks associated with using off-label medicines that are manipulated to enable administration to children. Prescribers need to be aware of the consequences of manipulating medicines formulations, particularly for drugs with a narrow therapeutic index, even in extemporaneous compounding by a pharmacist where there is insufficient evidence on product quality. In addition, healthcare professionals should be aware that patients and their carers often further manipulate medicines to aid in compliance, particularly within a paediatric population where 19% of all medicines administered to children were manipulated.[36]

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