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Review Article

A REVIEW ON ORO-DISPERSIBLE DOXYCYCLINE TABLETS

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ABSTRACT

Oral drug delivery remains the most preferred route for administration of various therapeutic agents. Novel ODT technologies address many patient and pharmaceutical needs such as enhanced life cycle management to convenient dosing particularly for pediatric, geriatric and psychiatric patients who have difficulty in swallowing (Dysphagia) conventional tablet and capsules. Technologies used for manufacturing of ODTs are either conventional technologies or patented technologies.Orodispersible tablets (ODTs), also known as fast melt, quick melts, fast disintegrating have the unique property of disintegrating in the mouth in seconds without chewing and the need of water. The aim for designing these dosage forms, convenient to be manufactured and administered, free of side effects, offering immediate release and enhanced bioavailability, so as to achieve better patient compliance. Though oral drug delivery systems, preferably, tablets are the most widely accepted dosage forms, for being compact, offering uniform dose and painless delivery. The present study demonstrated potentials for rapid absorption, improved bioavailability, effective therapy and patient compliance.

KEYWORDS :*ODTs , Dosage forms, Dysphagia, Efficacy, Pharmaceutical needs.*

INTRODUCTION

An ideal dosage regimen in drug therapy of my disease is the one which immediately attains the desired therapeutic conclusions of drug in plasma and maintain it constant for entire duration of treatment.[1] the drug may be administered by variety of routes of dosage forms. The oral route of drug administration is most popular and has been successfully used for conventional delivery of drugs. It offers the advantage of convenience, ease of administration, greater flexibility in dosage forms design, ease of production and low cost. Hence it is adopted wherever possible. It is probable that at least 90 % of all drug is used to produce systemic effects are administered by oral route.

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The dosage forms available for oral administration are liquid like solution, suspension emulsion & solids like powders, tablets & capsules. The physical state of most of the drug being solid, they are administered in solid dosage forms.[1]

Among the drugs that are administered orally, solid dosage form represents the predefined class of product. They are versatile, flexible in dosage strength relatively stable, present lesser problem in formulation and packaging and it is convenient to manufacture, store handle and use. Solid dosage forms provides best protection to the drug against temperature, humidity, oxygen light and stress during transportation of two solid dosage forms i.e. tablets and capsules. The tablets are in wide use.[2]

Tablets: [3, 4]

Tablets may be defined as solid pharmaceutical dosage forms containing drug substance with or without suitable diluents and

prepared by either direct compression or moulding methods.

Advantages of tablets:

- They are a unit dosage form and offer the greatest dose precision and the least content variability.
- Their cost is lowest of all oral dosage forms.
- They are lightest and most compact of all oral dosage forms.
- They are in general the easiest and cheapest to package and shipment of all oral dosage forms.
- They may provide the greatest ease of swallowing with the least tendency for "hang-up" above the stomach. Especially when coated, provided that tablet disintegration is not excessively rapid.
- They lend themselves to certain special release profile products such as enteric or delayed release products.
- They are better suited to large scale production than other unit oral forms.
- Tablets have the best combined properties of chemical, mechanical and microbiological stability.

Disadvantages of tablets:

- The major drawback for a tablet dosage form is that they are large in size.
- Some drugs resist compression into dense compacts owing to their amorphous nature or flocculent low density character.
- Drugs with poor wetting, slow dissolution properties, intermediate to large dosage or any combination of these features may be difficult or impossible to formulate and manufacture as a tablet that will still provide adequate or full delay bioavailability.
- Difficult for pediatric and geriatric patient swallow.

Types of tablets; [5]

- Compressed tablets
- Sugar coated tablets
- Film coated tablets
- Enteric coated tablets
- Multiple coated tablets
- Layered tablets
- Press coated tablets
- Controlled release tablets
- Buccal or sublingual tablets
- Tablets for solutions
- Molded tablets or tablet triturates
- Fast dissolving or disintegrating tablets

Methods of manufacturing: [3]

Tablets are manufactured by wet granulation, Dry granulation and direct compression method.

Wet granulation:

It is process in which a liquid is added to a powder in a vessel equipped with any of agitation that will produce agglomeration or granules. These granules are then compressed to form tablets. Most pharmaceutical tablets are processed by wet granulation, and yet it is the most complex means of tablet processing. The popularity of wet granulation is because it can be applied to all drugs, and for many formulators it is the method of choice for drugs with a high dose and a very low dose. Most product formulators see wet granulation as a universally applicable means of tablet processing. All of the required functionality of a compression mix – good flow, good compactability, uniform distribution of drug and controllable drug release – can be built in using wet granulation without relying on the intrinsic properties of the drug or the excipients. Additionally using wet granulation it is possible to get stabilising agents such as pH modifiers into close contact with the drug and so potentially maximize tablet stability. For high dose drugs, poor flow and compaction of the active mean that wet granulation may be the only feasible means of producing tablets, and for low dose drugs the granulation process is seen as being capable of "locking" drug into granules and thereby minimizing the potential for segregation and poor content uniformity.

Dry granulation:

In this technique, there is no use of liquids. The process involves the formulation of slug. Then the slugs are mixed and screened to produce granules. The granules are then compressed to form tablets.

Direct compression:

The term direct compression is used to define the process by which tablets are compressed directly forms powder blends of active ingredients and suitable excipients [including fillers, disintegrants and lubricants] which will flow uniformly in the die cavity and forms a firm compact.

Oro-dispersible dosage forms: [6]

Recent advances in technology have presented viable dosage alternative for patient who may have difficulty swallowing tablets or capsules. Traditional tablets and capsules administered with an 8-oz. glass of water may be inconvenient or impractical for some patients. For example a very elderly patient may not be able to swallow a daily dose of Antibiotic. An eight year old with allergies could use a more convenient dosage form than antihistaminic syrup.

A middle aged woman undergoing radiation therapy for breast cancer may be too nauseous to swallow her H2-blocker. Oro-dispersible dosage forms (ODT) are a perfect fit for all these patients.

ODT disintegrate and/or dissolve rapidly in the saliva without need of water. Same tablets are designed to dissolve in saliva remarkably fast within few seconds and are true fast dissolving tablets. Other certain agents to enhance the rate of tablet disintegration in the oral cavity and are more appropriately termed fast disintegrating tablets, as they may take up to a minute to completely disintegrate. Some drugs are absorbed from mouth, pharynx and esophagus as the saliva posses down into stomach. In such cases the bioavailability of drug is significantly greater than those observed from conventional tablet dosage form.

A dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter of seconds, when placed upon tongue". This system is recognized with other synonyms like fast dissolving tablets; melt in mouth tablets, porous tablets, rapidly disintegrating tablets quick dissolving and rapimelt tablets. Despite various nomenclatures the function and concept of all drug delivery system (DDS) is similar.

- Oro-dispersible tablet is tablet that is to be placed in mouth where it disperses rapidly before swallowing.
- The drug in the present study is Doxycycline Hyclate. It is an oral. It act as antibiotic.

Advantages of Oro-dispersible formulation: [7]

- Improved patient compliance is the primary benefit of this technology.
- Administration to patient who cannot swallow and patients who refuse to such as pediatric, geriatric and psychiatric patients.
- No need of water for swallowing the dosage forms. This is highly convenient release for the patients who are travelling or do not have immediate access to water.
- Added benefits of convenience and accurate dosing as compared to liquids.
- More rapid dry absorption through pre-gastric absorption from the mouth, pharynx and esophagus.
- Easily portable and suitable for transportation by patients.
- The fast dissolving dosage forms combines the benefit of liquid formulation with those of solid oral dosage forms.
- A wide range of drug can be considered as a candidate for this dosage forms.

Eg: Antipyretic, anti inflammatory agents, antibiotics, anti asthmatic agents, diuretics, anti arrythmatic, anti hypertensive.

Disadvantages of Oro-dispersible formulation: [7]

- Delayed absorbed at specific site cannot be given in these dosage forms.
- These tablets show high friability, less hardness than conventional tablets.

Characteristics of an Orodispersible tablets: [8]

Taste of medicament:

As most of drugs are unpalatable, Oro-dispersible drug delivery system usually contains the medicament in the taste masked. Delivery systems dissolve or disintegrate in the patient mouth, thus relaxing the active ingredients which come in contact with the

taste buds and hence taste masking of drug becomes critical for patient compliance.

Hygroscopicity:
Several Oro-dispersible Dosage forms are hygroscopic and cannot maintain physical integrity under normal conditions of temperature and humidity which calls for specialized product packaging.

Friability:
In order to allow Oro-dispersible Tablets to dissolve or disintegrate in oral and cavity they are made of either porous or compressed into Tablets with very low compression force, which makes the Tablet friable which are difficult to handle, often requiring specialized peel-off blister packing.

Desired criteria for Oro-dispersible Tablets (ODT):

Oro-dispersible Tablets should: [9]

- Not require water to Swallow but it should dissolve or disintegrate in the mouth in matter of seconds.
- Be portable without fragility concern
- Have pleasing mouth feel
- Leave minimal or no residue in the mouth after oral administration
- Exhibit low sensitivity to environmental conditions as humidity and Temperature
- Allow the manufacture of Tablet using conventional processing and packaging equipment as low cost.

Biopharmaceutical consideration for Oro-dispersible Tablets: [9]
When a new drug delivery system is introduced biopharmaceutical factors like metabolism and excretion must be considered.

Pharmacokinetics:
After absorption, the drug contains therapeutic level and elicits pharmacological effects. So both rate and extent of absorption is important. In conventional Dosage forms there is delay in disintegration and dissolution. While ODT rapidly disintegrates in oral cavity and dissolution is fast. Due to disintegration of ODT in mouth, absorption is started from mouth, pharynx and esophagus. Some factors like age, gastro intestinal pH, blood flow through GST are taken into consideration because elderly be considered as separate unique medicate population.

Drug disintegration:
It depends upon factors like,

- Binding of drug to tissue
- Perfusion state
- Tissue permeability
- Drug interaction
- Disease state

In geriatric patients decrease in lean body mass and total body water results in decreased volume of distribution (V_d) of liquid soluble drug.

Duration and intensity of action:
It depends upon factors like,

- Biotransformation
- Regional blood flow to liver
- Decrease in liver volume

Decrease in liver volume and regional blood flow to liver reduces the biotransformation of drug through oxidation, reduction and hydrolysis. Excretion by renal clearance as showed. Thus half life of renally excreted drugs increased.

Bioavailability of Oro-dispersible Tablets:
Disintegration and dissolution of ODT in oral cavity depends upon various factors like,

- Physiochemical properties of drugs
- Ingredients used for taste masking
- Method of manufacture

While manufacture batch to batch consistency should be ensured, patient's factors are also involved such as presence of amount of saliva in oral cavity and the extent of tongue movements etc. The disintegration time in-vivo can vary greatly depends on how the patient processes the drug product. The patient who actively moves the drug product with the tongue around the oral cavity experiences shortest disintegration time.

General properties of ODT: [10]

Excellent mouth feel:
Disintegrants has narrow particle size that imparts a smooth mouth feel to quick dissolve.

Large particles tend to result in a gritty mouth feel that many consumers find objectionable. Therefore, smaller particles which are not felt in the mouth are preferred. These benefits are especially important in ODT.

Taste :[11]

Tongue is responsible for taste. Different areas of tongue are responsible for different tastes like sweet, bitter, sour and salty. The sweet sensations are easily detected at the tip whereas bitterness is most readily detected at the back of the tongue. Sour sensation occurs at the side of the tongue, but salty sensations are usually detected at both the tip and at the side of the tongue. Western civilization recognizes only four basic tastes: Sweet, Sour, Salty and Bitter. The Japanese add fifth taste called Umami for monosodium glutamate. The high perception for bitterness may be an evolutionary defense mechanism that keeps us from swallowing poisons.

Anatomy and Physiology of taste:

In mammals, taste buds are aggregations of 30-100 individual elongated "neuroepithelial" cells, which is 50-60 microns in height and 30-70 microns in width. It is often embedded in specializations of surrounding epithelium, termed papillae. In the oral milieu the microvillar processes project through a small opening from the apex of the taste bud is called taste pore. There are afferent nerves present at the base of the taste buds. These afferent nerves invade the bud and ramify extensively. Each fiber of this nerve typically synapsing with multiple receptor cells within the taste bud. The Location of taste buds: The taste buds are found on three types of papillae on the tongue,

- A large number of taste buds are on the wall of the trough that surrounds the circumvallate papillae, which forms ‘v’ line on the posterior surface of the tongue.
- Moderate number of taste buds is on fungi form papillae over the flat anterior surface of the tongue.
- Moderate numbers are on the foliate papillae located in the folds along the lateral surface on the tongue.
- Additional taste buds located on the palate and few on the tonsillar pillars, the epiglottis and even in the proximal esophagus.

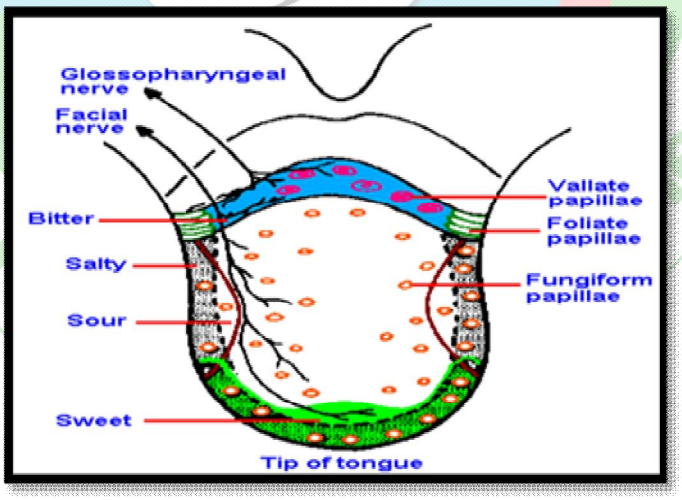

Figure 1: Physiology of the tongue

Physiology of taste:

Physiologically, taste is a sensory response resulting from a chemical stimulation of taste buds on the tongue. The sense of taste is conducted to the brain by a process called taste transduction. This process begins with the interaction of tastant (i. e., food or medicine) with receptor cells in the taste buds. The

tastant binds with G-protein coupled receptors in the cells, triggering the release of gustducin. Taste sensation begins when gustducin activates the effector enzymes phosphodiesterase 1a or phospholipase C β-2. The effector enzymes then change the intracellular levels of second messengers such as cyclic adenosine monophosphate (cAMP), inositol, 1,4,5-triphosphate (IP3), and idacylglycerol (DAG). The second messengers activate ion channels, including calcium channels inside the cells and sodium, potassium and calcium channels on the extracellular membrane. This ionization depolarizes the cell, causing the release of neurotransmitter that send a nerve impulse to the brain that carries the signal of taste.

Chemistry of taste:

Sour:

Sour stimuli in foods, such as vinegar (acetic acid), lemon (citric acid), and apple (malic acid) are easily identifiable. All sour substances contain acids that generally ionize in aqueous solutions to produce hydrogen ions. Therefore the higher the concentration of hydrogen ions, the stronger is the sourness. Sour taste is not only dependant on hydrogen ions, but also on lipid solubility. A higher lipid solubility of acids provides for greater concentrations as taste receptors, accounting for the increase in sour sensation.

Salty:

It has been shown that cationic species are partially responsible for the salt solutions. Sodium chloride has a typical salty taste. Chlorides of potassium, ammonium and calcium have a typical salty taste, but their solutions taste differently. Most halide salts (sodium chloride, sodium bromide, potassium chloride and sodium iodide) have a dominating salty taste. Potassium bromide and ammonium bromide have a salty, bitter taste but potassium iodide is intensely bitter, which indicates that the taste sensations of salts shift to bitterness as molecular weight increases.

Sweet:

Sweet taste is produced by wide variety of compounds, many of which do not have any apparent structural similarity. The two most common sweet substances, sugars and glycerin are polyhydric alcohols containing $–CH_2OH$ groups, which contributes significantly to sweetness. Saccharin which has no –OH group, is intensely sweet but has bitter after taste. In contrast, naturally occurring glycosides are bitter. Some amino acids, for example, glycine are sweet. The sodium and calcium salts of cyclohexylsulfamic acid (cyclamates) and the dipeptide ester aspartame is roughly thirty times sweeter than sugar and has been used as sugar substitute.

Bitter:

A bitter taste, like sweet taste, is commonly found in a wide variety of compounds, most of which are salts of organic and inorganic compounds. Bitterness is often associated with the nitro group, and the presence of two or more nitro groups in a molecule results in a bitter taste. Structurally unrelated compounds, such as esters of aromatic acids lactones and sulfur containing aliphatic compounds exhibit bitterness.

Taste masking:

As more than 50% of pharmaceutical products are administered orally, undesirable taste is one of the important formulation problems that can be encountered with certain drugs. Oral administration of bitter drugs with acceptable level of palatability is a key issue for health care providers especially with paediatrics and geriatric patient. Thus, elimination or reduction of bitterness is an important issue during design of oral pharmaceutical formulations.

An ideal taste masking process and formulation should have the following properties:

- Rapid and easy to manufacture.
- Involves least number of equipment.
- Requires minimum number of excipients for an optimum formulation.
- Has no adverse effect on drug bioavailability
- Requires excipients that are economical and easily available.
- Least manufacturing cost.

Methods of Taste Masking: [12, 13]

In order to eliminate or reduce bitter taste of orally administered pharmaceuticals various techniques and strategies are adopted by pharmaceutical scientist. These strategies are classified as below:-

Sensory approaches:

- Using flavoring and sweetening agent inhibiting bitterness
- Numbering of taste buds

Complexation and absorption:

- Complexation with ion-exchange resins formation of inclusion
- Complexes with β-cyclodextrin derivatives
- Adsorption of drugs into clays or other adsorbents wax embedding of drugs.

Chemical approaches:

1. Formulation of products
2. Formulation of different salts

Barrier approaches:

- Using viscosity modifiers
- Using emulsions
- Using liposomes
- Using microspheres

Fast disintegration:

When introduced into water disintegrants, which is used in ODT. Quickly wicks water into its capillaries and swell which results in rapid disintegration. The disintegrants particles are granular and highly porous. This porous particle morphology allows for better wicking of liquid into the particle and Tablets. This sugar disintegrants polymer does not form gels. This could retard drugs release or results in summary texture.

Tablets hardness:

To achieve rapid disintegration, ODT are often porous and have low hardness and high friability. As a result there can be a high level of tablet breakage unless special packaging systems are used. Therefore the challenge is to develop formulation with rapid disintegration and robust physical properties due to its unique particles morphology, the super disintegrants is a highly compressible material that increases Tablet hardness and reduces friability.

An ODT system comprises low moisture that is convenient for doing suitable for labeling and easy packing, handling and application. At the same time the rapid hydration rate facilities on almost immediate softening of the ODT upon application in the oral cavity. The friability and strength of the Tablet may be selected / modified to facilitate automatic rewinding, die punching and packaging during manufacturing.

Mechanism of drug release:[9]

The drug release from ODT is due to the action of super disintegrating like crosprovidone, sodium starch glycolate and polyvinyl pyrolidone in the formulation.

Super disintegrants provides quick disintegration due to combined effect of swelling and water absorption by the formulation as an effect of swelling of super disintegrants. The wetted surface of the carrier increases, and promotes the wettability, dispersability of the system and there by enhance the disintegration and dissolution.

Basic approaches of designing ODT: [8]

To ensure the Tablet fast dissolving attribute. Water must quickly egress into the Tablet matrix to cause rapid disintegration and instantaneous dissolution of the Tablet.

This can be achieved by,

- Maximizing porous structure of the Tablet matrix
- Incorporating the appropriate disintegrating agent.

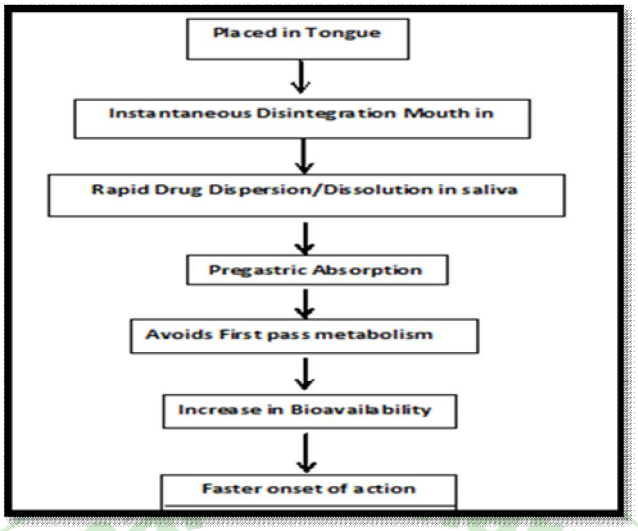

Figure 2: Mechanism of Oro Dispersible tablet

Patented technologies: [7, 8, 9]

Zydis technologies:

This technology is based on forming an open matrix network. A zydis tablet is produced by lyophilizing or freeze drying the drug in a matrix usually containing gelatin desetrin or alginates. Water is used during the process to produce the porous units for rapid disintegration when the formulation contact with saliva. Preservatives suspending agents and pH adjusting excipients may be added if necessary. Collapse protectants like glycine prevent the shrinkage the zydis units. This unit has poor stability at higher temperature and humidities. It rapidly absorbs water and is very sensitives to degradation at humidity's greater than 65%.

Wowtab technology:

Wow means "without water". This technology combined with low and high moudability saccharine to produce fast dissolving tablets. During production the tablet is maintain its hardness, and its physical character unit is comes in contact with saliva. The wowtab product dissolves quickly in 15 seconds.

Flash dose technology:

The flash dosesforms utilize the shear form technology in association with conform. This technology is used to eliminate the bitter taste of medicament. During shear form process, a crystalline, granular powder of mixed polysaccharides is converted into amorphous fibers, termed as floss. By applying controlled crystallization, the floss can be converted into crystalline structure with very high specific surface area and correspondingly rapid rates of dissolution. The major drawbacks of these dosage forms are that the tablets are highly friable, soft and moisture – sensitive. To protect these, specialized packaging is required. This dosage form accommodates drug up to 600 mg.

Durasolv technology:

Durasolv is second- generation fast dissolving / disintegrating tablet formulation, Durasolv is the patented technology of CIMA labs. The tablets made by this technology consist of drug, filler and a lubricant. Durasolv has much higher mechanical strength due to the use of higher compaction pressures during tabletting. It is produced in a faster and more cost-effective manner. Durasolv is so durable that it can be packaged in either traditional blister packaging or vials.

One disadvantage of Durasolv is that the technology is not compatible with larger doses of active ingredient, because the formulation is subjected to much higher pressures on compaction. The drug powder coating in Durasolv may become fractured during compaction, exposing the bitter tasting due to patients taste buds. Therefore Durasolv technology is best suited for formulation including relatively small doses of active ingredient.

Orasolv technology:

CIMA labs have developed Orasolv technology. This technology utilizes the effervescences material and taste masked active ingredients and requires only conventional manufacturing process and equipments. The concept of effervescences is well known formulation art utilized in several dosage forms. However the current technology uses their concept in a modified fashion where the micro particles are prepared by novel technique involving dispersion of active ingredients into suitable polymer dispersion together with other excipients such as mannitol and magnesium oxide. Orasolv dosage forms have been developed, containing active drug and multiple ingredients in a tablet. Tablet produced by this technology are soft and friable and hence packaged using an integrated packaging line that uses a specially designed robotic pick and pack system.

Flashtab technology:

This technology is yet another fast dissolving / disintegrating oral tablet formulation. It utilizes most of same excipients as in conventional compressed tablets.

A disintegrating agent and a swelling agent are used in combination with coated drug particles in this formulation to produce a tablet that disintegrates in the mouth in one minute.

Table 1: Commercially available Oro-Dispersible tablets

Technology	Active Ingredient	Category	Trade Name	Manufacture
Freeze Drying	Pyrexia	Antirheumatic , non-steroidal	Feldene Fast Melt	Pfizer Inc. NY. USA
	Loratidine	Antihistamine	Claritin Redi Tab	Schrring Plough Crop. Kenilworth USA
	Rizatriptan	Antimigraine	Maxalt MLT	Merk& Co., NJ USA
	Olanzapine	Antipsycotic	Zyprexia	Eli Lilly
	Famotidine	Antihistimne	Pepcid RPD	Merck & Co., NJ
	Zolmitriptan	Antimigraine	Zoming-ZMT	Astra Zeneca, Wilnington
Disintegrant Addition	Acetaminophen	Antipyretic	Tempra Quickies	Bristol Myers
	Paracetamol	Antipyretic	Febrectol	Prographarm, France.
Sugar Based Excipient	Diphenhydramine & Pseudoephedrine	Antiallergic	Benadryl Fast Malt	Warner Lambert, NJ, USA

SUMMARY AND CONCLUSION

It was concluded that an Oro-dispersible tablets and dosage form offer many advantages for drugs having absorption. Tablets are almost certainly the most cost-effective and efficient form of dispensing medicines. The tablet provides a versatile, compact, robust and accurate platform for drug delivery. While the functional versatility of the tablet as a dosage form has been appreciated for decades, the design versatilityof the tablet has historically been underappreciated. A variety of shapes can provide distinction without compromising manufacturing requirements.

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