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A REVIEW ON FORMULATION AND EVALUATIONOF ORODISPERSIBLE BILAYER TABLET CONTAINING FENOPROFEN CALCIUM

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ABSTRACT

he aim of this paper was to conduct a study of the development and evaluation of fenoprofen-containing mouth dissolving anti-inflammatory tablets. MDT is a strategy for increasing patient compliance. By solving previously encountered administration problems and leading to the extension of patent life, orodispersible drug delivery systems (ODDDS) have built a significant market position. In today's scientific setting, drug delivery technology has become extremely competitive and is rapidly evolving in response to rising demand. Fast dissolving tablet (FDT) is one form of revolutionary and unique drug delivery device that is quickly gaining traction in the rapid dissolving technology research sector. Orodispersible tablet (ODT) is a form of tablet that dissolves or disintegrates quickly in the mouth saliva without the use of water. Bilayer tablet will provide the drug in two portions- first layer will provide 25% of drug for pregastric absorption and second layer provide 75% of drug for gastric absorption. Tablet will be prepare by applying partly internal and externaladdition of superdisintegrants. Many drawbacks, such as dysphagia or lack of access to water when driving, have been addressed by this innovative drug delivery such as ODT or MDT (mouth dissolving tablet). FDT may also be a good alternative to traditional dosage forms. The different techniques used to prepare ODT, silent functionality, various proprietary technologies, and the process of super disintegration, as well as the challenges and limitations, are all discussed in this review article.

KEYWORDS: Oral route, Orodispersible tablet, Bilayer, Super disintegrants, Dysphagia, fenoprofen.

INTRODUCTION

The first drug administration devices used traditional dosage types. The oral route of drug administration is the most commonly used and approved. Oral dosage forms are commonly used due to their ease of use and low cost as opposed to other dosage forms.[1] However, it has some disadvantages, including dysphasia (difficulty swallowing), poor bioavailability, and a delayed onset of action. To address these concerns, researchers have long looked at using the "oral cavity" to improve the drug's permeability and bioavailability. Since the mucosal lining is less keratinized in the buccal mucosa[2], the "oral cavity" has strong permeability. The drug enters systemic circulation directly via the jugular vein, ensuring a rapid onset of action, avoidance of first pass metabolism, and drug degradation in the gastric region and enzymatic hydrolys is in the intestine.[3] "ODT (Oral Dispersible Tablet) can spread or disintegrate in less than 3 minutes when put on tongue," according to the European Pharmacopoeia. The quick dissolving drug delivery system (FDDDS) is a relatively new concept that blends the benefits of both liquid and solid formulations while also offering advantages over conventional dosage types. Swallowing tablets is difficult for many patients, particularly the elderly. One such example is a rapidly disintegrating/dissolving tablet, which disintegrates quickly or dissolves completely in the mouth.[4] The orodispersible tablet (ODT) is the most commonly preferred commercial product among the various dosage forms produced to improve the ease of administration. Fast melting, fast dispersing, rapid dissolve, rapid melt, and or quick disintegrating tablet are all terms used to describe the ODT. The Food and Drug Administration (FDA) classifies all MDTs as orally disintegrating tablets.

The word orodispersible tablet was recently coined by the European Pharmacopeia to describe a tablet that disperses or dissolves in the mouth in less than 3 minutes before being swallowed. Patients can quickly swallow such a tablet because it disintegrates into smaller granules or melts in their mouth from a hard solid to a gel-like structure.[5] Orally disintegrating tablets are particularly useful for children and the elderly. Some drugs' bioavailability may be increased by oral absorption or pregastric absorption from saliva that passes down into the stomach.

Synthetic and natural Mucilage, cross-linked carboxymethyl cellulose (croscarmellose), sodium starch glycolate (primogel), poly vinyl pyrollidone, and other superdisintegrants have

instant tablet disintegration and make it easier to design a delivery system with desirable characteristics.

These formulations are commonly recommended for emergency medications, such as cardiac agents, asthma, brain stroke, anti-hyperlipidemia, and so on.

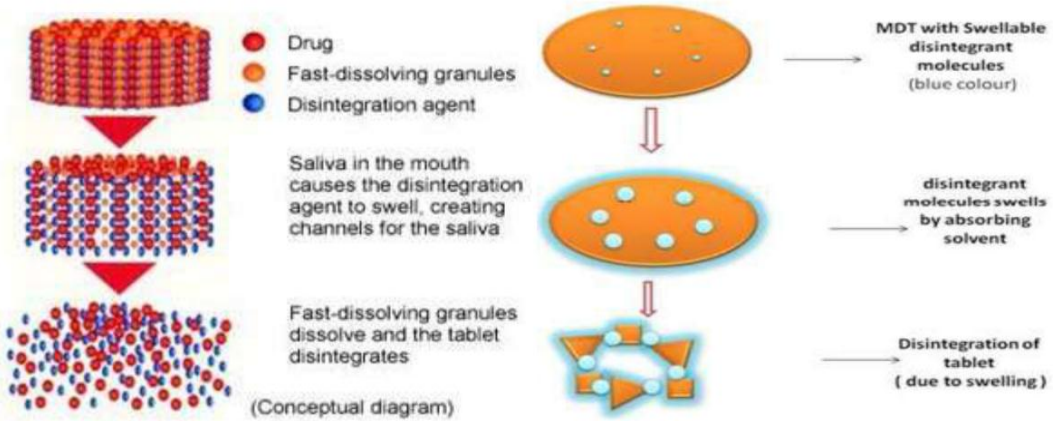

Figure 1: Mechanism involved in ODT.

Need of Oral Route of Administration

The oral route of administration remains the most favoured route for a variety of reasons, including ease of ingestion, relatively low manufacturing costs, packaging, shipping improved stability, avoidance of discomfort, flexibility, and, most importantly, patient compliance. Immediate and modified release oral drug delivery systems are the two types. Immediate release drug delivery systems are designed to disintegrate quickly and release drugs instantly.They are linked to rapid increases and decreases in drug plasma levels, resulting in reduced or lost drug efficacy as well as an increased risk of side effects.[6]

Ideal Properties of Odt

Oral administration requires no water, but they dissolve, scatter, and disintegrate in the mouth in a matter of seconds. Get a nice taste in your mouth. Have a taste masking capacity that is appropriate. Make a deliberate effort to be more tenacious and not easily swayed After administration, leave little to no residue in the mouth; show no sensitivity to environmental factors (temperature and humidity). Allow tablet production to be done with standard processing and packaging equipment.[7]

Advantages of Odt

Rapid drug therapy intervention for patients who cannot swallow, such as the elderly, stroke victims, bedridden patients, and patients who refuse to swallow, such as paediatric, geriatric, and psychiatric patients. Pregastric absorption of drugs from the mouth, pharynx, and oesophagus as saliva passes down results in improved bioavailability/rapid absorption. The ability to change the perception of medication as a bitter pill, particularly in paediatric patients, is aided by the good mouth feel property.[8]

Drug (Fenprofen)

Fenoprofen is a non-steroidal anti-inflammatory medication (NSAID). Rheumatoid arthritis, osteoarthritis, and mild to severe pain can all benefit from fenoprofen calcium. Nalfon is a brand name for fenoprofen sold in the United States. It inhibits the activity of cyclooxygenase (COX) and prostaglandin synthesis, which reduces inflammation, pain, and fever.[10]

Super Disintegrants Used In Odts

Superdisintegrants are low-concentration disintegrants that have a higher disintegration efficiency and are more efficient intragranularly. The swelling pressure exerted in the outer or radial direction causes the tablet to burst or the rapid absorption of water, resulting in a massive increase in the volume of granules to facilitate disintegration.[11]

Various types of Super disintegrants used are as follows –

- Crosspovidone
- Microcrystalline cellulose
- Sodium starch glycollate
- Sodium carboxy methyl cellulose or ross
- Carmelose sodium
- Crosscarmellose sodium
- Calcium carboxy methyl cellulose
- Modified corn starch.
- Sodium starch

Table: 1. Superdisintegrants.

Sr. No.	Name	Description	Trade Name
1	Modified cellulose (Croscarmallose.NF)	Sodium carboxy methyl cellulose which has been cross-linked to render the material insoluble	Ac-Di-Sol, Nymcel, Solutab
2	Modified starches (Sodium starch glycolate.NF)	Sodium carboxy methyl starch, the carboxymethyl groups induced hydrophilicity and cross-linking reduces solubility	Explotab, Primojel
3	Cross-linked Polyvinylpyrrolidone (Crospovidone)	Crosslinked Polyvinylpyrrolidone, high molecular rending the material	Crospovidone, Kollidon, Polyplasdone

Methods of Incorporating Disintegrants Into Tablets

There are three techniques of incorporating disintegrating agents into the tablet as described below:

- **Internal Addition (Intra-granular):** Until wetting powder mixtures with granulating fluid, the disintegrant is thoroughly mixed with a few other powders in this process. As a result, the granules contain the disintegrant.
- **External Addition (Extra-granular):** The disintegrants are mixed into the sized granulation before compression in this process.
- **Partly Internal and External:** In this process, a portion of the disintegrant is inserted internally and a portion is added externally, resulting in an immediate interruption of the tablet into previously compressed granules, while the disintegrating agent inside the granules produces extra material. In addition to powder particles, granules suffer from attrition. Starches have a high propensity for water and swell when wet, making it easier to crack the tablet matrix; this action is due to capillary action in tablets. The starch's spherical form raises the tablet's porosity, which encourages capillary action. Cellulose and gums have a greater tendency to swell when exposed to water, breaking the tablets into smaller fragments. The addition of tartaric acid and citric acid to sodium carbonate, sodium bicarbonate, potassium bicarbonate, or calcium carbonate as an alternative method for tablet disintegration is a viable choice. When they come into contact with water, they emit carbon dioxide, which causes the tablet to become unstable.[12]

The Need For Development of Odts

These include the following:

- Patients who have trouble swallowing or chewing solid dosage types, such as children and the elderly.
- Patients who are afraid of choking and refuse to take a solid preparation.
- Elderly patients who may be unable to swallow an antidepressant on a daily basis.
- A patient who is experiencing constant discomfort and is on a trip or has little or no access to water.[13]

Effectiveness Factor

These formulations appear to have improved bioavailability and a quicker onset of action. In situations where the drug dissolves rapidly, dispersion in saliva in the oral cavity allows pregastric absorption from certain formulations. Many medications are absorbed in the buccal, pharyngeal, and gastric regions.[14]

Manufacturing and Marketing Factors

A new dosage form enables a manufacturer to expand market exclusivity, exclusive product differentiation, value-added product line extension, and patent protection by providing a more convenient dosage form to its patient population. This raises income while still concentrating on underserved and under-treated patient groups. In response to a generic challenge filed in the United States by Ranbaxy, Eisai Inc. introduced Aricept ODT, a line extension of donepezil for Alzheimer's disease, in Japan in 2004 and the United States in 2005. When marketers have a new, easier-to-take type that meets the needs of an underserved patient population, they improve their brand and company profile.[15]

Challenges In Formulating Odts Palatability

The medicament is typically in a taste-masked form in orally disintegrating drug delivery systems. Patients' oral cavity disintegrates or dissolves delivery mechanisms, releasing active ingredients that come into contact with taste buds; hence, taste-masking of drugs becomes vital to patient enforcement.[17]

Mechanical Strength

To allow ODTs to disintegrate in the oral cavity, they are either made of very porous and soft-molded matrices or compressed into tablets with very low compression force, which

makes the tablets friable and/or brittle, difficult to handle, and often necessitates specialised peel-off blister packaging, which can add to the cost.[18]

Hygroscopicity

Several orally disintegrating dosage formulations are hygroscopic, which means they can't keep their physical integrity under normal temperature and humidity conditions. As a result, they require humidity control, which necessitates the use of specialised product packaging.[19]

Drug Concentration

The amount of medication that can be introduced into each unit dose limits the application of ODT technologies. The drug dose must be less than 400 mg for insoluble drugs and less than 60 mg for soluble drugs in lyophilized dosage types. When creating fast-dissolving oral films or wafers, this parameter is especially difficult to control.[20]

Aqueous Solubility

Water-soluble drugs present a number of formulation challenges due to the formation of eutectic mixtures, which cause freezing-point depression and the formation of a glassy solid, which can collapse upon drying due to the lack of supporting structure during the sublimation process. The use of matrix-forming excipients like mannitol, which can cause crystallinity and thus impart rigidity to the amorphous composite, can often prevent such collapse.[21]

Size of Tablet

The easiest size of tablet to swallow is 7-8 mm, while the easiest size to handle is one larger than 8 mm, according to research. As a result, finding a tablet size that is both easy to take and easy to manage is challenging.[22]

Selection of Odt Drug Candidates

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 are considered ideal for ODT formulations.

ODT was developed by researchers for a variety of drugs used in therapy that involve a rapid peak plasma concentration to achieve the desired pharmacological response. Neuroleptics, cardiovascular agents, analgesics, antiallergics, anti-epileptics, anxiolytics, sedatives, hypnotics, diuretics, anti-parkinsonism agents, anti-bacterial agents, and erectile dysfunction medications are only a few examples.[23]

Conventional Techniques Used For Preparation of Oddds

Because of its simplicity and cost-effectiveness, the disintegrant addition technique is a common technique for formulating Fast-dissolving tablets. The basic concept involved in formulating orodispersible tablets using the disintegrant addition technique is the addition of superdisintegrants in the required concentration to achieve rapid disintegration while preserving a nice mouth feel. To prepare quick dissolving tablets, microcrystalline cellulose and low substituted hydroxypropylcellulose were used as disintegrating agents in the ratios of 8:2–9.1. By raising the porosity of agar through water treatment, it is used as a disintegrant in the production of rapidly disintegrating tablets. Taste-masked granules and a mixture of excipients consisting of crystalline cellulose (Avicel pH 02) and low-substituted hydroxypropy cellulose HPC, LH-11) were used to make rapidly disintegrating tablets of the bitter drugs oxybutynin and pirenzepine. Direct compression was used to create rapid oral disintegration tablets using a co-ground mixture of D-mannitol and crospovidone. CIMA labs patented Orasolv technology, which uses the disintegration mechanism of carbon dioxide or effervescence in the formulation of fast-dissolving tablets.

OraSolv is an oral dosage type that blends taste-masked drug ingredients with an effervescent excipient framework that dissolves quickly. Microencapsulation, which coats or entraps the active compound in an immediate release matrix, is used to mask the taste.

The effervescent excipient mechanism assists in rapid tablet disintegration, enabling pharmaceutical ingredients to be swallowed until they come into contact with the taste bud. The OraSolv tablet dissolves easily without chewing or water, allowing for successful taste masking of a wide range of prescription and nonprescription active drug ingredients.[25]

Freeze Drying

After the substance has been frozen, water is sublimated from it. Lyophilization is a pharmaceutical technology that enables heat-sensitive drugs and biologicals to be dried at a low temperature under sublimation conditions. Lyophilization produces highly soluble preparations with a high specific surface area that dissolve easily and have improved absorption and bioavailability.[27]

Moulding

Molded tablets are made using water soluble ingredients in this process, allowing the tablets to dissolve completely and easily. The powder mixture is moistened with a hydro-alcoholic

solvent before being formed into tablets at a lower pressure than typical tablet compression. After that, the solvent is extracted by air drying. Compressed tablets are much more lightweight than moulded tablets. These have a porous structure that makes them dissolve faster.[28]

Spray-Drying

Spray drying can produce highly porous and fine powders that dissolve rapidly. Hydrolyzed and non-hydrolyzed gelatins are used as supporting agents, mannitol is used as a bulking agent, sodium starch glycolate or crosscarmellose sodium is used as a disintegrating agent, and an acidic and/or alkali substance (e.g. sodium bicarbonate) is used to improve disintegration and dissolution. Tablet compressed from the spray dried powder disintegrated within 20 seconds when immersed in an aqueous medium.[29]

Direct Compression

It is the simplest method of producing tablets. Direct compression uses standard equipment, widely available excipients, and a small number of processing steps. The disintegration and solubilization of directly compressed tablets is based on the individual or combined acts of disintegrants, water soluble excipients, and an effervescent agent. Patented Technologies for Tablets that Dissolve in 10 to 14 Minutes Zydis Technology is a company that specialises in technology. The first marketed new technology tablet was Zydis, the most well-known of the fast-dissolving/disintegrating tablet preparations. After being held on the tongue for a few seconds, the tablet dissolves in the mouth. A Zydis tablet is made by lyophilizing or freeze-drying the drug in a gelatin matrix. Since the product is so light and delicate, it must be distributed in a special blister pack. Patients should be told that instead of pushing the tablets through the foil film, they should peel it back to release the tablet. The Zydis product is formulated to dissolve in 2 to 3 seconds on the tongue. Since the final water concentration in the freeze-dried product is too low for microbial growth, the Zydis formulation is also self-preserving.[31]

EVALUATION OF POWDER PROPERTIES OF TABLET

The various characteristics of blends tested are as given below[31]

1. Angle of Repose

The angle of repose can be used to calculate the frictional force in a loose powder. The maximum angle possible between the surface of the powder pile and the horizontal plane is established. Newman's funnel approach was used to evaluate the angle of repose.

Angle of repose is determined by the following formula Tan? = h/r Therefore = Tan-1 h/r Where?

=Angle of repose h = height of the cone r = Radius of the cone base Angle of Repose less than 30 ° shows the free flowing of the material.

2. Compressibility index (Carr's index)-

Percent compressibility of granules as determined by Carr's compressibility index was calculated by the following formula:

$$\text{Carr's index} = \frac{TD - BD}{TD} \times 100$$

Where-

TD- Tap density

BD- Bulk density

Table 2: Flow properties as indicated by Carr's index.

Percent compressibility	Type of flow
5-15	Excellent
12-16	Good
18-21	Fair to passable
23-25	Poor
33-38	Very poor
>40	Extremely poor

3. Bulk Density

The term "density" refers to the amount of weight per unit volume. Bulk density, abbreviated as pb, is defined as the mass of the powder divided by the bulk volume and is measured in grammes per cubic centimetre. The bulk density of a powder is primarily determined by particle size distribution, particle form, and particle adhesion. Bulk density can be classified into two groups. The particles are packed such that wide gaps exist between their surfaces, resulting in a light powder with a low bulk density. The smaller particles are pushed between the larger particles, resulting in a dense, heavy powder. Bulk density has a big impact on the size of containers required for raw material and blend handling, shipping, and storage.

A sample of about 50gm (blend) is carefully introduced in a 100ml graduated cylinder.

(i) The cylinder is dropped onto a hard wood surface three times from a height of 1 inch at two second interval.

The bulk density is then obtained by dividing the weight of sample in gms by final volume in cm

(ii) Pb=M/ Vp Where p b =Bulk Density" M = Weight of sample in gm V = Final volume of blend in cm 3

(iii) Bulkiness Specific bulk volume or reciprocal of bulk density is called bulkiness or bulk. Bulkiness increases with a decrease in particle size. In mixture of material of different sizes, however the smaller particle shifts between the larger particles and tends to reduce the bulkiness.

The bulkiness can be calculated by the following formula Bulkiness= I/ p b where, p b = Bulk Density. Loose bulk density It is defined as the ratio of weight of blend in gms to the loose bulk volume (untapped volume) in cm 3 Loose bulk density is given by Loose bulk density p u = Weight in gms / V b Where V b = Bulk volume (untapped volume)

(iv) Void Volume- The volume of the spaces is known as the void volume "v" and is given by the formula V=Vb-Vp Where Vb = Bulk volume (volume _ before tapping) V = True volume (volume after tapping)

(v) Porosity The porosity € of powder is defined as the ratio of void volume to the bulk volume of the packaging. The porosity of the powder is given by €= Vb - Vp/ Vp =1- Vp/Vb Porosity is frequently expressed in percentage and is given as %€ = (1 - Vp/ Vb) X 100 The porosity of powder indicates the types of packaging a powder undergoes when subject to vibrations, when stored, or in tablet machine when passed through hopper or feed frame.

4. Hausner's Ratio (HR) - It is the ratio of tapped density to the bulk density.

It is given by - HR=TD/BD

TD- Tapped density, BD- Bulk density

Table 3: Flow properties as indicated by Hausner's ratio.

Hausner's Ratio	Flow of powder
1-1.2	Free Flow
1.2-1.6	Cohesive Flow

Evaluation Test For Fast Dissolving

Tablets from all the formulation were subjected to following quality control test.[30]

1. Size and Shape

Dimensionally identifying, tracking, and manipulating the tablet's size and shape is possible.

2. Tablet thickness

Tablet thickness is a crucial factor in both reproducing appearance and counting with filling equipment. The standardised thickness of the tablets is used as a counting device in some filling equipment. A micrometre was used to measure the thickness of ten different tablets.

3. Uniformity of weight I.P.

Twenty tablets were taken and their weight was measured individually and collectively on a digital weighing balance, as per the procedure for weight uniformity. The collective weight was used to calculate the average weight of one tablet. The weight variance test will be a good way to figure out how uniform the drug content is.

4. Disintegration test

We learned if a dosage type would disintegrate in a certain amount of time when put in a suitable liquid medium under the specified experimental conditions by conducting a disintegration test. The end point of the Disintegration test is when no trace of the tablet exists on the measuring apparatus's screen, or if there is, it consists of bits of the tablets' insoluble coating.

5. *In- vitro* dissolution studies

This test is performed to measure the length of time taken by a dosage type to reach to the systemic circulation in the body. This test is carried out under specific condition.

Method: First, we'll need 1000 mL of dissolution media, which can be found in the dissolution apparatus. The dissolution medium must then be heated to between 36.5 and 37.5 degrees Celsius. Then, before spinning the paddle, allow the tablet to be placed in the dissolution apparatus.

We must use a suitable system to hold the tablet in the bottom of the pot during this process; otherwise, the dosage type would float to the surface. It's important to note that air bubbles aren't allowed to form on the surface of the dosage form. The in-vitro dissolution analysis should be completed as soon as possible at 75 rpm. Withdraw a sample from the dissolution basket within the defined time period, or as the time assured, the withdrawal sample should not be less than 10ml, except in the case of single sampling, in which case we must add an

equivalent volume of dissolution media to the volume of sample taken out from the dissolution basket. The in-vitro dissolution test should be performed according to the instructions in Table 5.14. Rep the method five times more. Using a suitable spectroscopy tool, measure the percentage of the active pharmaceutical component dissolved in the solution for each dosage type dissolution examination.

Table 4: Acceptance Table for Dissolution.

Period	No Tested	Approval Criteria
S1	6	Every element should not be less than E* + 5%
S2	6	Average of 12 elements (S1 +S2) must be equivalent to Or greater than E, and no elements should be less than E -15%.
S3	12	Average of 24 element (S1+S2+S3) should be equal to or greater than E, not more than 2 units should be less

*E = Total of dissolved active ingredient precise in individual monograph, articulated as percentage of assured quantity.

Recognized criteria for Dissolution: In case results do not match with the criteria area given in acceptance Table for Dissolution (table-4) continue the test with extra dosage forms (tablets) through stages S2 and S3 unless the result conformed.

CONCLUSION

Tablets that dissolve quickly are called modern dosage types. Improved effectiveness, fast onset of action, increased bioavailability, and patient compliance. There are several branded products in this group that have recently been launched. MDT's key selling point is its ability to disintegrate easily in the oral cavity without the use of water, as well as its mechanical efficiency. Because of this, this formulation is a perfect option for geriatric and paediatric patients. Due to advancements in scientific research and the discovery of new excipients, ODT is projected to expand at a tremendous and rapid rate in the near future, resulting in a future-ready, combative arena of pharmaceutical drug delivery systems. As compared to traditional oral dosage forms, orally disintegrating tablets may have better patient acceptance and enforcement, as well as improved biopharmaceutical properties, effectiveness, and protection. ODTs are becoming more commonly available as over-the-counter medications to combat allergies, colds, and flu symptoms.

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