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Review Article

Orodispersible Tablet in Treatment of Migraine: Opportunities, Challenges and Recent Advancements

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Abstract

The most comfortable and choicely path of drug administration is oral route. Orodispersible tablets bring a revolution among all routes of drug administration as well as oral route of drug administration also. Orodispersible tablets are unit dosage form but it has unique characteristics. It disintegrates in the mouth within a minute for the presence of saliva where the presence of super disintegrates in the preparation. Especially, old and child have no chance to swallow as a result it is very acceptable for them. Migraine is a very well-known irritating condition for adult and female. Migraine is a debilitating and common neurovascular illness associated with symptoms of one-sided headache, nausea with or without vomiting, photophobia and/or phonophobia. But these symptoms are subjective and vary from patient to patient. Orodispersible tablets are most important solution of migraine like emergency condition and helping human by transferring from hell to heaven. Very short half-life, quick disintegration, quick onset of action and better bioavailability brings the orodispersible tablets into the top position of the management of migraine. Sumatriptan, zolmitriptan like drugs are helping their hands to reduce migraine. Lastly, there are lots of drugs are investigating for this purpose and our hope that the orodispersible tablet can give the pioneer and will give the migraine free era to us and our futures.

Keywords: Orodispersible tablet, migraine, sumatriptan, super disintegrate, fast dissolving

INTRODUCTION:

The oral route considered to be most popular and widely used route of administration because of its benefits, such as ease of administration, manufacturing cost, pain avoidable and importantly patient compliance. However conventional oral dosage form, i.e., tablet & capsule having swallowing difficulties, known as dysphagia. These problems are associated among all age group especially Pediatric and geriatric patient[1]. Orodispersible tablet is solutions for these limitations as this formulation dissolve rapidly when placed in mouth and doesn't require to chewing or drinking water. United States Food and Drug Administration (FDA) define ODTs as solid dosage forms that disintegrate in few seconds in saliva when they placed in oral cavity. However, European Pharmacopoeia (EP) has termed ODTs as uncoated tablets that disintegrate quickly within 3 minutes when placed in mouth. Orodispersible mini tablet is another type of new approach for Pediatric use. They are similar to Orodispersible tablet but smaller in size (2-4 mm) depending upon the age group and active substances[2].

MIGRAINE: AN OVERVIEW

Migraine is a debilitating and common neurovascular illness[3] associated with symptoms of one-sided headache, nausea with or without vomiting, photophobia and/or phonophobia[4]. But these symptoms are subjective and vary from patient to patient. However, A special sort of focal neurologic visual condition known as aura, affects one out of every three migraine patients[5]. The major reason of the pain is due to the dilation of brain blood vessels and subsequently constricts as stimulation of nerve endings occurs near the affected blood vessels. However, whether migraine is caused by a vascular or neurological problem, the specific reason is still unknown[6]. It's been known for a long time that migraine has a strong hereditary component. Genetic research on rare monogenic subtypes, commonly well known as familial hemiplegic migraine, has revealed new information about the disease's pathophysiology. According to a recent data gene involved in ion transport at synapse and glutamatergic transmission (CACNA1A, ATP1A2 and SCN1A) casually mutate, leads to development of this ailment[7].

Migraine can broadly classify into two major types: (i) migraine with aura and (ii) migraine without aura. Migraine with aura (also known as classical migraine) symptoms of the sensory or other central nerve systems are frequently grouped together and appear and gradually develop to form headache or other symptoms of migraine. This is recurrent and lasting for minutes. Whereas migraine without aura is common type and can last anywhere from 4 to 72 hour. The common symptoms include nausea and/or vomiting, photophobia, aggressiveness in routine behavior,

phonophobia and headache in one side with pulsation [8] . The treatment of migraine is depending up on the subject history, frequency and age. For adults NSAIDs and triptans are most effective in treating acute migraine. For primary treatment NSAIDs are used. However, though it is a first line therapy but, in many cases, it becomes fail to achieve patient's initial clinical compliance. This led to use of triptans. While selecting a drug for treating migraine, formulation consideration is always prior. As the nasal and parenteral route of administration options are limited as well as they are not fulfilling the patient compliance. As a result, oral medicine administration is the only choice[9] .

CRITERIA FOR DEVELOPMENT OF ODTS IN MIGRAINE

Drug's Perspective[10]

- Prolonged action drugs are not suitable.
- Drugs having unpleasant taste are not suitable.
- Drugs with higher dosing frequency and very short half-life are not acceptable.
- Drugs indicating changes in their pharmacokinetic characteristic with compare to their conventional dosage forms are not compatible for Orodispersible dosages forms.
- Drugs that produce higher number of toxic metabolites after first pass metabolism in liver and drugs having poor absorption property from oral cavity are not ideal to develop this type of drug delivery system.
- Drugs capable of spreading and partition through an upper GIT epithelium (log P>1 or preferred > 2) and those capable of permeating oral mucosal tissue are considered suitable for Orodispersible formulation.

Patient's Perspective [11]

- The tablet should be disintegrated within a certain period of time (less than 30 sec).
- Patient having Sjogren syndrome and as well as those are having less saliva secretion are not compatible for Orodispersible drug delivery.
- The oral cavity should have no to minimum residue after administration.
- The size of the formulation should be satisfactory with respect to patient compliance.

Dosages Form Design [12,13]

- The dosage form should be design in such a way that water intake doesn't required.
- The mechanical strength should be optimum that the formulation starts to disintegrate within a certain period of time.
- The onset of action should be quick to give response.
- It should be able to stay intact during the formulation process and should stay withstand to a wide range of temperature and humidity.

ADVANTAGES OF ORODISPERSIBLE TABLET IN TREATMENT OF MIGRAINE [14-16]

- Administration is easy and chances of chocking are very less especially for geriatric and Pediatric as doesn't required to swallow the tablet.
- Water doesn't require instead of that saliva present in the mouth helps to disintegrate.
- Patient doesn't require to chewing the tablet.
- This drug delivery system exhibits rapid action due to its quick disintegration and fast dissolving property.
- Bioavailability of drug increases as it avoids hepatic metabolism.
- Condition like acute migraine where patients suffer from nausea and/or vomiting. It is very beneficial.
- Masking of the drugs having bitter taste is performed, thus it produces a good mouth feel and improve the patient compliance.
- Nasal route is another way of drug administration but however there are several factors including drug retention time & nasal mucosal permeability, while ODTs are free from this factors [5] .
- Manufacturing of Orodispersible tablet can be performed through the existing machinery, used in the preparation of conventional tablet.

PROCESS OF DISINTEGRATION [2,17] :

Bioavailability is always a key factor of a formulation. Orodispersible tablet has higher bioavailability compared to oral conventional solid dosage forms as its bypass the first pass-metabolism. Orodispersible formulation contains the maximum amount of medication and it gets absorbed in oral mucosa. The disintegration process of Orodispersible tablet is representing in a schematic way in the given figure (**Fig. No. 01**). Tablet in contact with water starts to disintegrate. Disintegrating agent present in the formulation in contact with saliva present in the mouth starts to swell and create pores that cause water to penetrate and tablet starts to break. The drugs get dissolved and start to absorbed through oral mucosa. However, there are certain unseen mechanisms that cause the orodispersible pills to dissolve and further dissolved. They are: Swelling, Wicking, Repulsion and Deformation.

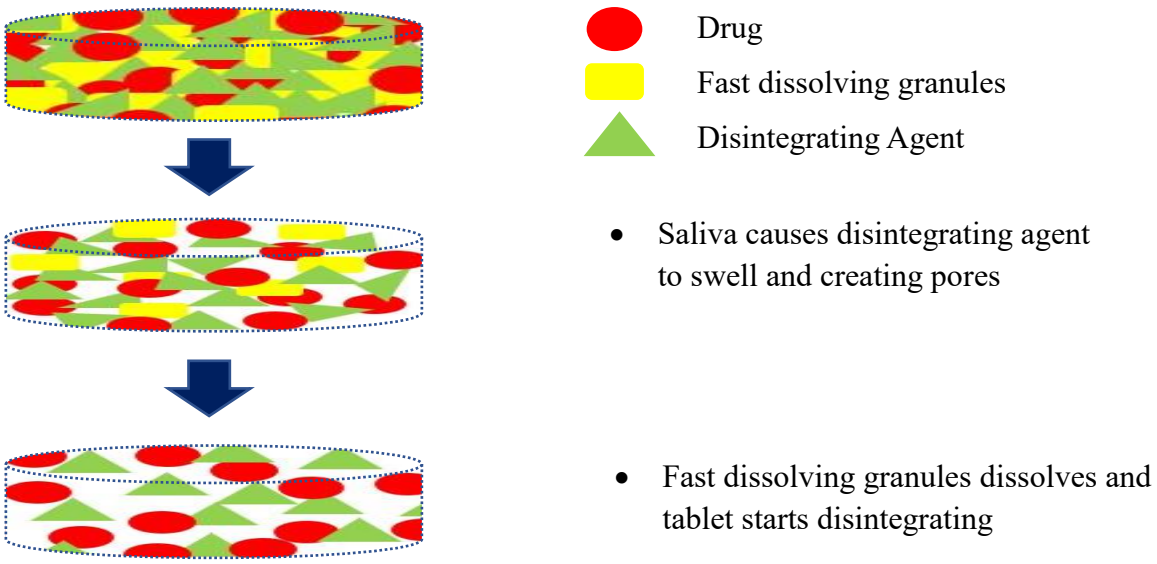

Figure 1: Schematic diagram of disintegration process [2,17]

MECHANISM OF DISINTEGRATION FOR ORODISPERSIBLE TABLET [18-20]:

Tablet disintegration follows four basic mechanisms. They are a) Swelling, b) Wicking, c) Repulsion, d) Deformation.

a) Swelling: The mechanism involves for this is based upon the 'swell'. Not all but majority of super disintegrating agent works by this mechanism. Super disintegrating when comes in contact with saliva in mouth, the adhesiveness of the aqueous phase overcome the other excipients to extras force on super disintegrating agent resulting swelling of the tablet and falling a part of it. The swelling is depending upon the porosity of the tablet. Low porosity helps to achieve adequate swelling force and shows better disintegration comparing to tablet having higher porosity. It is also notable that if porosity become too much low then water cannot penetrate hence the disintegration is become poor again.

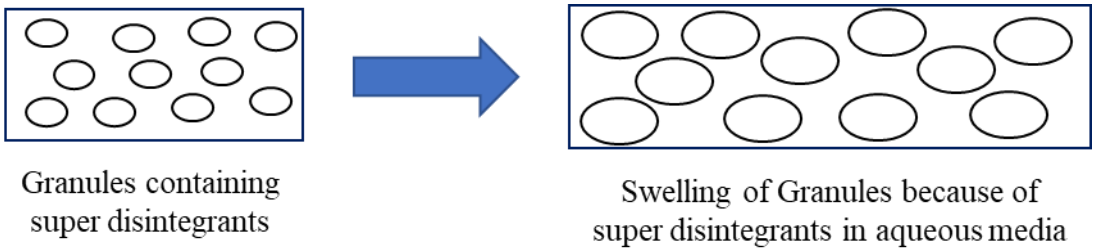

Figure 2: Diagrammatic representation of mechanism of swelling [18]

b) Wicking: This mechanism is based on the "wicking" or capillary action, occurred due to penetration of aqueous media into the tablet. This penetration causes reduction in the interparticle bond and thus resulting the breakage of tablet into fine particle. The drug -excipient. Maintaining adequate porous structure is important for disintegration as it formed a hydrophilic network within the drug particle.

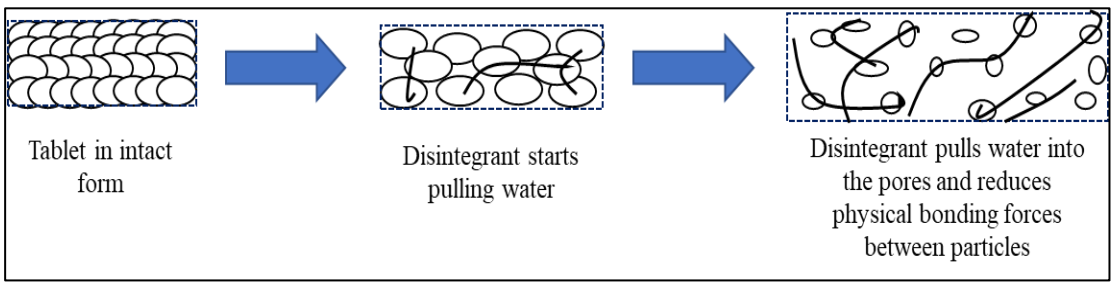

Figure 3: Diagrammatic representation of mechanism of wicking [19]

c) Repulsion: This disintegration mechanism based on a repulsion theory proposed by Guyot-Hermann. This theory observed that "non-swellable" disintegrating agent can also cause tablet to disintegrate. The disintegration process is caused by the repulsion forces of current between two particles, and water is necessary to generate these forces. The pores allow the liquids especially water is passing and causes breakdown of Hydrogen bond as well as the other forces that hold the tablet together.

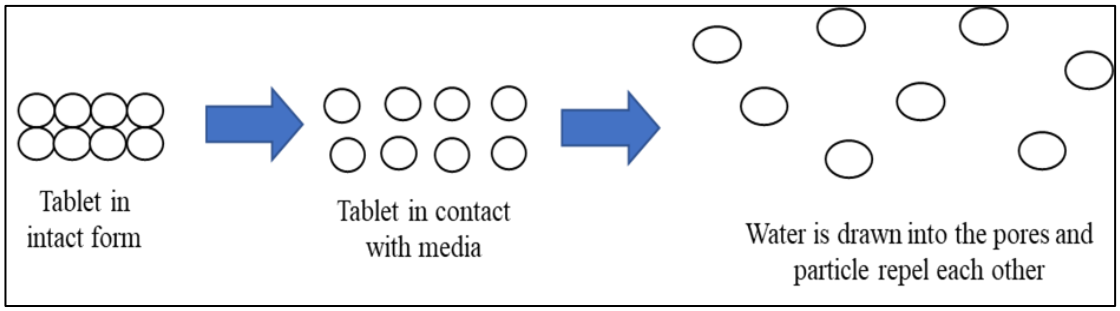

Figure 4: Diagrammatic representation of mechanism of repulsion [20]

e) Deformation: This mechanism involves that disintegrate particle get deformed during the process of tablet compression and return to its normal structure in contact with water. Starch grains are widely considered to "elastic" in nature, meaning by removal of pressure it will return to original shape which was collapsed under pressure. However, grains thought to have collapsed more permanently due to compressional force involves during the tablet punching. These grains are "energy rich" and will release the energy on contact with water. In simple word starch grains having gone through deformation have better disintegration property compare to normal starch grains.

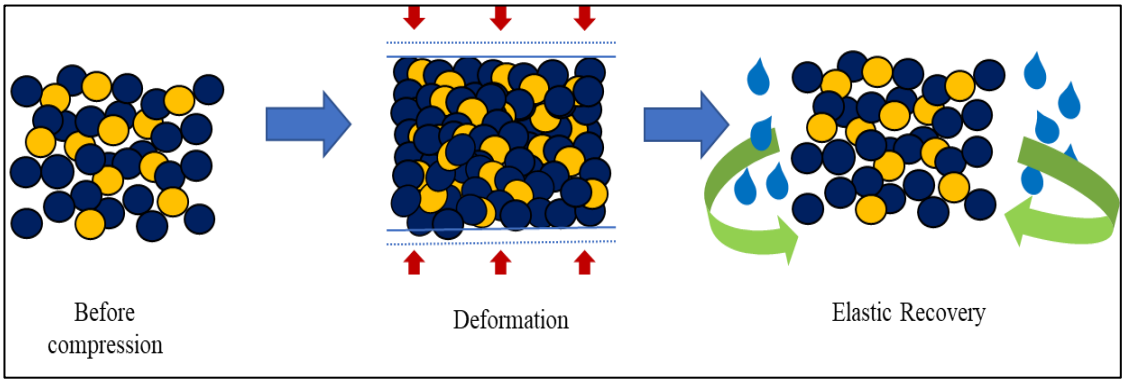

Figure 5: Diagrammatic representation of mechanism of swelling [20]

TECHNIQUES FOR PREPARING ORODISPERSIBLE TABLET [18,21]

Among all techniques available for preparation, below mentioned techniques are major and widely used in the preparation of Orodispersible tablet or mouth dissolving tablet. They are:

a) Freeze drying or Lyophilization
b) Tablet Molding
c) Spray drying
d) Sublimation
e) Direct Compression
f) Mass Extrusion
g) Cotton candy Process
h) Fast Dissolving Film

a) **Lyophilization/Freeze Drying:** It is a technique that is used to prepare Orodispersible Tablet. The basic concept is to remove the solvent from the prepared solution that were kept in freezing temperature to produce an amorphous porous structure that dissolve quickly [11].

This technology allows heat sensitive drugs to dry under low temperature by applying vacuum. The drug mixture is prepared by incorporating the drug into the polymeric solution. Then the blister pack that has already been created is poured using the drug mixture. Blister pack containing trays are passed through the nitrogen passage containing liquid nitrogen that will freeze the solution. The blister packs are continuing to freeze by putting them in the cold cabinet of the refrigerator to complete the process [22].

b) **Tablet Molding:** Tablet molding can be done by two methods. Solvent molding method and Heat molding method.

Solvent Method: Solvent method is performed by moistened the blend using hydroalcoholic solvent. Then the

blend is molded into tablet under lower pressure compare to conventional tablet compression. Air drying method is applied to remove the solvent. Finally, Porous structures are formed that promote dissolution due to less compaction compare to conventional tablet [19].

Heat Method: In heat molding method, a suspension is prepared containing drug, sugar and agar as solidifying agent. Then the suspension is poured into blister pack. At room temperature agar is solidified and a jelly like structure is formed. Subsequently it is dried at 30° C in vacuum condition [23].

c) **Spray Drying:** This method is based on a particulate support matrix. In this technique for supportive agent of matrix, gelatin (hydrolyzed and nonhydrolyzed) is used. Mannitol is used for bulking purpose and for disintegration process of the formulation sodium starch glycolate or croscarmellose are used. The suspension prepared from ingredients is spray-dried to get fine powder [24].

d) **Sublimation:** The rapid disintegration of Orodispersible tablet is depends up on the porous structure. Improve in porosity will lead to increase in disintegration time. Sublimation is a process where the porosity increases by using volatile substances such as camphor [25].

Volatile substances incorporated with the drug and excipients. Then the blend is compressed. Evacuation of Volatile material occurred. Porous structure is formed by applying heat [12].

e) **Direct Compression:** This is the most popular, cost effective and simple technique used for tablet preparation. In this technique drug-excipients mixture is prepared and directly compressed to prepare a tablet. The concentration of super-disintegrants is key factor to achieve desired disintegration time. Poor flow property of dug can causes problem during compression, so selection of drug is also an important factor [26].

f) **Mass Extrusion:** The principle involves in this technology is to softening the blend by using mixture of water-soluble compounds like Polyethylene glycol, methyl alcohol and removal of soften mass through the extruder or syringe to instigate a barrel of the object into even parts using warmed sharp edge to form a tablet. Coating of granules can be done for masking the unpleasant taste by utilizing the drying chamber [27].

g) **Cotton Candy Process:** As the name suggests this process uses a distinctive spinning mechanism to create a crystalline structure identical to floss that mimics cotton candy. This method involves concurrently melting and spinning polysaccharides or saccharides to generate a matrix. The matrix form is partially recrystallized to increase flow characteristics and compressibility. After that, it is milled, blended, and combined with the active components. There after it is proceed for compression to form Orodispersible tablet [28]

LIST OF PATENTED TECHNOLOGIES [29,30,31]

Table 1: Patented technologies[29]

Patented Technologies	Basic Process	Developed By
Zydis	Lyophilization/Freeze Drying	R.P. Scherer, Inc.
Orasolv	Direct Compression	Cima Labs, Inc.
Quicksolv	Lyophilization/Freeze Drying	Janssen Pharmaceuticals
Durasolv	Direct Compression	Cima Labs,Inc.
Wowtab	Direct Compression	Yamanouchim Pharma Tech. Inc.
Flashtab	Direct Compression	Prographarm Group
Flashdose	Cotton Candy Process	Fuisz Technology, Ltd.
Oraquick	Micromask, taste masking	KV Pharm.Co., Inc.
Lyoc	Lyophilization/Freeze Drying	Cephalon Corporation

Other patented technologies include Frosta, Pharmabrust, Quick-dis, Nanocrystal technology. Frosta and pharmabrust technologies followed compression tecniques and developed by Akina Inc. and SPI Pharma Inc. respectively. Quick-dis is a solvent casting method and developed by Lavipharm laboratories Inc. while Nanocrystal technology developed by Elan (King of Prussia) and it followed lyophilization technique.

CHALLENGES IN FORMULATION OF ODTS IN TREATMENT OF MIGRAINE [32-34] :

Mechanical Strength:

Mechanical strength and disintegration time is proportional to each other. Increase in mechanical strength will cause increase in the disintegration time and poor mechanical strength may cause breakdown of tablet during packing transportation or handling. So, maintain an optimum mechanical strength is important.

Taste Masking:

ODTs are disintegrate in oral cavity so the drugs releases after the very next time by touching with the taste buds, hence good pleasant taste is required. For the unpalatability of the drugs, results it is necessary for taste masking by using taste masking agent.

Mouth Feel:

After disintegration the particles produced in oral cavity must be tiny as possible. There should be no or very minimal

residue leave after oral administration of ODTs. Addition of additives like menthol can enhance the mouth feel.

Environmental Sensitivity & Hygroscopicity:

It should not be sensitive to environment factor such as humidity and temperature. Basically, ODTs are hygroscopic in nature so a specialized product packaging is used to protect it from humidity.

Aqueous Solubility:

Water-soluble drugs face numerous formulation problems as they have tendency to form eutectic mixtures, resulting in depression of the freezing point and they create clear solid that can collapse in the ongoing time of the sublimation process due to loss of supporting structure.

Size of Tablet:

The administrations become patient compliance when the size of the tablet is suitable. The easiest tablet size to swallow is stated to be 7-8 mm while another greater than 8 mm is easiest to handle. As a result, finding a tablet size that is easy to use, take and handle is tough.

PROGRESS OF ODTS IN TREATMENT OF MIGRAINE

Sumatriptan

Gugulothu *et al.* developed and characterized sumatriptan Orodispersible tablet by freeze drying technology. The formulation composition was optimized and evaluate on basic parameters including size, shape, content uniformity, mechanical strength, wetting time, *in-vitro* and disintegration time. The study revealed that formulation containing gelatine and mannitol in 3.75% W/V and 3.5% W/V respectively had shown disintegration time of less than 10 secs. In-Vitro dissolution study also suggested that 90% of the drug releases within 10 mins from the dosages form [35].

Munija *et al.* investigated and prepared immediate release tablet of sumatriptan succinate tablets by sublimation method followed by direct compression technique. The main objective was to reduce the lag time and provide better onset of action. The study showed that formulation containing 8% W/V croscarmellose sodium and 10% W/V menthol have significant disintegration time of 18 secs [36].

Zolmitriptan

Spierings *et al.* performed a double-blind, parallel-group trial on Zolmitriptan. The study was performed to determine the duration of response taking Zolmitriptan 5 mg ODT with placebo. The results showed a significant reduce in headache from moderate or severe to mild or no headache at 30 mins. With zolmitriptan 5mg ODT, significantly more patients experienced a prolonged headache response over 24 hours compared with placebo. At all timepoints (0.5, 1, 2 hours of post dose), zolmitriptan 5 mg ODT provided a greater pain-free rate than placebo, with the differences becoming substantial at one hour [37] .

Rizatriptan

Cady *et al.* performed a randomized, placebo-controlled, double-blind, factorial design study with rizatriptan 10 mg ODT. 91% (188 out of 207) patients treated a study migraine. In comparison to placebo, patients using rizatriptan reported significantly better pain relief at 2 hours (66.33%). Significantly, there was also pain relief sustain for patients (52.2%) after 24 hours with rizatriptan 10 mg ODT [38] .

Dungarwal *et al.* prepared an orodispersible tablet of rizatriptan using β cyclodextrin by direct compression method. The formulation was optimized and prepared tablets were evaluated. The optimized formulation showed a significant disintegration time of 35 secs [39].

Almitriptan

Alladi *et al.* formulated and evaluated ODT by granulation followed by direct compression containing almitriptan as a potent drug. Eudragit EPO and Precirol a to 5 were used as taste masking agents. The results showed a significant disintegration time of 15 secs and *in-vitro* drug release was 90% after 15 mins [40].

Naratriptan

Kshirasagar *et al.* prepared and evaluated naratriptan ODT by direct compression technique. The formulation was optimized and formulation containing 5% W/V of crospovidone and 4% W/V of croscarmellose sodium had showed a disintegration time of 7-8 secs. In-vitro dissolution study suggested that drug releases more than 90% in 10 mins [41].

EVALUATION OF ODTS [32,42,43] :

ODTs are evaluated on various parameter including hardness, friability, weight variation, drug content etc. Apart from these, conventional evaluation tests are also performed to evaluate the effectiveness of ODTs including dissolution study, disintegration time, wetting time, water absorption ratio, etc.

Hardness: An adequate range of hardness always difficult to achieve for ODTs. The hardness always kept in a lower range for faster disintegration. The hardness test is performed using conventional hardness tester.

Friability: Friability of a tablet can be determined by using conventional friabilator, i.e., Roche friabilator. The instrument rotates at 25 rpm and tablet is placed. After 100 revolutions the tablets is reweighted and calculate the % friability using the formula.

% Friability = Loss in weight / Initial Weight * 100

Weight variation: Weight variation is the deviation of average weight of each sample and individual weight of each sample. It is always calculated in percentage.

Drug content: Drug content assay is performed using UV-Spectroscopy. Random samples are powdered to dissolve in a suitable solvent and then absorbance is checked by taking the solvent as blank.

Dissolution study: In-vitro dissolution study carried out using USP type II apparatus at 50 rpm commonly. However, as the ODTs have very faster dissolution time so, slower paddle speed may be utilized. pH of 6.8 buffer can be used for this and concentration at different time interval is calculated.

Wetting time: For wetting time study a petri dish of 10 cm diameter is required containing 10 ml of water. Now the sample tablet is placed onto a tissue paper of 10 cm and then transfers it into the petri dish. The time required by water to reach the upper surface is the wetting time.

Water absorption ratio: The water absorption ratio study performed using the same procedure of wetting time. After water reach the upper surface the sample tablet is reweighted and calculated using the formula,

Water absorption Ratio (R) = $(V_b - V_a)/V_a * 100$

Where, V_b is the weight after absorption and V_a is the weight before absorption.

Disintegration time: Sample tablet is placed in conventional disintegration test apparatus at 37 ± 0.5°C and water is taken as media. The time required for complete disintegration process is recorded in seconds. Artificial saliva of pH 6.8 can also be used as media depending on the formulation.

LIST OF COMMERCIALLY AVAILABLE ODT PRODUCTS USED IN TREATMENT OF MIGRAINE [44,45]

Table 2: List of commercially available ODT products used in treatment of migraine [44, 45]

Market Name	Active Ingredients	Associated Company
Nurtec ODT	Rimegepant	Biohaven Pharmaceuticals
Zomig Rapimelt	Zolmitriptan	Gruenthal
Prozotil-MD	Prochlorperazine Maleate	Lifecare Neuro Products Ltd.
Mirtazapine ODT	Mirtazapine	Teva Pharmaceuticals
Maxalt-MLT	Rizatriptan Benzoate	Merck & Co. Inc.
Zomig-ZMT	Zolmitriptan	Astra Zeneca
Prozinn-MD	Prochlorperazine Maleate	Orion Lifesciences

RECENT ADVANCEMENT IN ODTS IN TREATMENT OF MIGRAINE [46]

Recently, a new ODT formulation of rimegepant has been approved by the FDA (Food and Drug Administration). This rimegepant drug molecule is antagonist to CGRP (citonin gene - related peptide) receptor. It has been found to be affected for migraine with aura and migraine without aura.

The clinical study was performed in two double-blind trials; the efficacy of rimegepant was assessed for patients with a 1-year history of migraine (with or without aura) and 2-8 moderate or severe migraine headaches each month. After the development of a moderate or severe migraine headache, patients were given either a single dosage of rimegepant 75 mg or a placebo. The results showed that after two hours patients with rimegepant had a significant relief from pain.

CONCLUSION

In modern era, ODTs are emerging as an alternative to treat migraine patient. The property including rapid disintegration without water and free from swallowing making it suitable for migraine patients having symptoms like nausea and/or vomiting. At any scenario, such as, patient travelling without water can also intake this. The advantages like improved bioavailability, rapid action, easy administration, self-medication, and patient compliance giving it an edge over conventional solid dosages form. However, research is going on to formulate ODTs for new drugs that are used in treatment of migraine. So, as a result ODTs can be a pioneer for effective and successful migraine therapy.

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CONFLICT OF INTEREST:

The authors report no conflict of interest.

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