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FORMULATION AND CHARACTERIZATION OF FAST DISSOLVING TABLET ALONG WITH ANTIEPILEPTIC DRUG

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ABSTRACT

Fast dissolving tablets emerge as one of the popular and widely accepted dosage forms, especially for pediatric patients because of incomplete development of the muscular and nervous system and a case of geriatric patients suffering from Parkinson's disorder or hand tremors. Few solid dosage forms like capsules and tablets are present days facing the problems like difficulty in swallowing (dysphagia), resulting in many incidences of non-compliance and making the therapy ineffective. Oral dosage form and oral route are the most preferred route of administration for various drugs has limitations like first-pass metabolism, psychiatric patients, bedridden and uncooperative patients. FDTs are disintegrating or dissolve quickly in the saliva without a need of water. Fast dissolving tablets are designed to dissolve in saliva remarkably faster, within a few seconds (less than 60 seconds), and those are real fast-dissolving tablets. FDTs formulations contain super disintegrants to enhance the disintegration rate of a tablet in the buccal cavity. FDTs have advantages such as easy portability and manufacturing, accurate dosing, good chemical and physical stability and an ideal alternative for geriatric and pediatric patients. FDTs have disintegrated quickly, absorb faster so, *in vitro* drug release time improve and this property of drugs (dosage form) enhanced bioavailability. FDT formulations have the advantage of both conventional tablet formulation and liquid dosage form. There are several technologies that are conventional or patented based on spray drying, cotton candy process, sublimation, melt granulation, direct compression freezes drying/lyophilization, phase transition process, mass extrusion, etc. have been developed for manufacturing of FDTs. In this review contain brief information about FDTs including definition, advantages, needs or requirements of FDTs, salient features of

FDTs, limitations, challenges to developing FDT, marketed formulations of fast dissolving tablets, etc.

KEYWORDS: Pediatric, geriatric, dysphasia, Fast Dissolving Tablets, saliva, buccal cavity, lyophilization, mass extrusion.

INTRODUCTION

Today's basic need is the requirement of drugs into its presentable form. The mean of drug delivery system is the dosage forms, used for application in to a living body. There are various types of dosage like tablets, syrups, suspensions, injections, suppositories, transdermal and patches having a different type of mechanism of drug delivery. All these classical as well as the modern dosage forms have various advantages and some disadvantages as well. So it's a big challenge for the pharmacist to develop an ideal drug delivery system in present scenario. To achieve the desired therapeutic effect, it's necessary that the drug should be reached to its specific site of action at a rate and concentration to show less adverse effects and maximum therapeutic effect. A thorough study of physicochemical principles should be done before the development of a suitable dosage form.[1]

Almost 50-60% of total dosage forms and administered via the oral route of drug administration. For the ease of administration, self-medication, accurate dosage, painless method and for patient compliance solid dosage forms are most popular. The most popular solid oral dosage forms are tablets and capsules, difficulty in swallowing may be the drawback with this dosage forms in some of the patients.[2]

More often the problem of swallowing is more common in pediatric patients due to fear of choking, dysphasia, and hand tremors. Due to underdeveloped muscular and nervous system and in schizophrenic condition in young patients. Near about one-third population has swallowing difficulties, which leads the poor patient compliance. So to overcome this problem rapidly dissolving tablets in oral cavity has a great deal of attention.[3]

United States Food and Drug Administration (USFDA) defined fast dissolving tablet (FDT) as "a solid dosage form containing a medicinal substance or active ingredient which disintegrate rapidly usually within a matter of seconds when placed upon the tongue".[3]

In the late 1970s fast dissolving drug delivery systems were first developed as an alternative to conventional dosage forms for the pediatric patient. These tablets are rapidly disintegrate in saliva within 60 seconds.[5]

To fulfill these medical needs, pharmaceutical technologists have developed a novel oral dosage forms known as orally disintegrating (dispersible) tablets (ODTs) or Fast disintegrating (dissolving) tablets (FDTs) or mouth melting tablets (MMTs) or mouth dissolving tablets(MDTs), immediate release tablets which disintegrate rapidly in saliva, usually in a matter of seconds, without the need to take water. Mouth dissolving tablets are formulated mainly by two techniques first use of super disintegrants like Croscarmellose sodium, sodium starch glycolate and crospovidone. Another method is maximizing pore structure of the tablets by freeze drying and vacuum drying.[5]

The direct compression method should be preferred for the formulation of such type of tablets because this method is quick, and cost effectiveness.[1]

Due to absorption of such drugs in oral cavity the bioavailability of such drugs may be increased. So that the first pass metabolismof these drugs is reduced as compare to standard tablets.[5]

Epilepsy is a neurological disorder, its first line treatment is administration of anti-epileptic drugs, which may be classified as- first, second and third generation of antiepileptic drugs.

Examples of few drugs according to their class as- First generation antiepileptic drug- Phenytoin, Phenobarbital, Carbamazepine, Valproic acid, Clobazam and Zonisamide. (Considered as second line drug in North America and Europe).

Third generation antiepileptic drug- Lacosamide and Eslicarbazepine acetate. Others recently delivered are included in the second generation. Post-second-generation antiepileptic drugs are commonly known as new antiepileptic drugs. In Japan, their administration as add-on therapy was approved in 2006 and gabapentin, topiramate, lamotrigine, levetiracetam, and rufinamide are distributed as oral drugs. Vigabatrin, oxcarbazepine, perampanel, and LCM are being considered for approval by the Japanese Ministry of Health, Labour, and Welfare.

In the definition of epilepsy revised in 2014 by the International League Against Epilepsy, the condition was defined as a disease of the brain manifesting any of the following

conditions: (1) at least two unprovoked (or reflex) seizures occurring more than 24 hours apart; (2) one unprovoked (or reflex) seizure with the probability of further seizures similar to the general recurrence risk of at least 60% after two unprovoked seizures occurring over the next 10 years; and (3) *a diagnosis of an epilepsy syndrome.*

While the new AEDs are not superior to traditional AEDs in terms of their antiepileptic- and acute adverse effects,[12-14] their prolonged administration elicited fewer adverse effects and milder interactions with other drugs than did traditional AEDs.[15-17]

Most new AEDs involve less teratogenicity and their effect on the patients' physical status, including hormone secretion and the bone and lipid metabolism, are milder.[19]

The lower teratogenicity of LTG and LEV has raised interest in these drugs. The new AEDs also offer favorable side benefits with respect to concurrent diseases and conditions.[20]

Several new AEDs have unique binding sites, LEV binds to synaptic vesicle 2 (SV2), PER to the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor, and LCM to collapsin response mediator protein-2 (CRMP2). The possibility that their unique profiles render the new AEDs advantageous for combination therapy has been suggested.[16]

As it is expected that new AEDs will be prescribed widely, cognizance of their basic mechanisms of action and their specific characteristics is important. This review presents an outline for the use of these drugs in adult epileptics based on the pharmacological activity of the new generation of AEDs, and discusses clinical indications for the use of these new drugs.

Seizure Classification

More than 40 distinctive epileptic signs have been recognized and generally classified into partial and generalized seizures. The partial seizures report for about 60 percent of all epilepsies and usually are due to a lesion in some part of the cortex, tumors, trauma, developmental malformations, stroke, and infections. Partial seizures are related with electrical discharge that begins locally and often remains localized. Partial seizure may generate relatively simple signs without loss of consciousness, such as involuntary muscle contractions, autonomic discharge or abnormal sensory experiences or, they may cause more complex effects on consciousness, mood and behavior, often termed psychomotor epilepsy. In psychomotor epilepsy, which is often related with a focus in the temporal lobe, the attack

may consist of stereotyped movements such as rubbing or tapping movements, or much more complex behavior like walking, dressing, or hair-combing.

The seizure generally lasts for a few minutes, after which the patient get wells with no memory of the event. The manners during the seizure can be bizarre and convoyed by a strong emotional response. The generalized epilepsy report for approximately 40 percent of all epilepsies and etiology is normally genetic. Generalized seizures involve the entire brain, as well as the reticular system, thus generating abnormal electrical activity throughout both hemispheres. Instant loss of consciousness is feature of generalized seizures. The major categories are tonic-clonic seizures (grand mal) and absences (petit mal). A tonic-clonic seizure consists of an initial powerful contraction of the entire musculature, genereting a rigid extensor spasm. Respiration prevents and micturition, defecation, and salivation are often occurs. The tonic phase lasts for about one minute and is followed by a series of violent synchronous jerks that slowly finishs in about 2-4 minutes. The patient continues unconscious for a few more minutes and then slowly recovers, feeling ill and confused. Injury may happen during the convulsive episodes. Absence seizures occur in children; they are much less dramatic but may occur more regularly than tonic-clonic seizures.

The patient suddenly ceases whatever he/she was doing, occasionally stopping speaking in mid-sentence, and stares blankly for a few seconds, with slight or no motor disturbance. With optimal drug treatment, epilepsy is prevented completely in about 75 percent of patients, and about 10 percent continue to have seizures at gaps of one month or less, which severely interrupt their life and work. Therefore need to improve the efficacy of therapy.

Common mechanism of action of antiepileptic drugs. Three major mechanisms of action are recognized.

Modulation of voltage-gated ion channels; enhancement of γ-aminobutyric acid (GABA)-mediated inhibitory neurotrans- mission; and attenuation of glutamate-mediated excitatory neurotransmission.[25]

Voltage-gated ion channels: Ion channels regulate the flow of positively and negatively charged ions across neuronal cell membranes and ultimately control the intrinsic excitability of the CNS. Voltage-gated Na+ channels are responsible for depolarization of the nerve cell membrane and conduction of action potentials across the surface of neuronal cells. At nerve

terminals, voltage-gated Ca+ channels are recruited by Na+ channel dependent depolarization, leading to Ca+ entry, NTM release and chemical signaling across the synapse. Ca+ channels are distributed, on a cellular and anatomical basis.

The AEDs (e.g., PHT, CBZ, valproate (VPA), lamotrigine (LTG) involves the prolongation and and closing of inactivation gate of Na+ ion channels, therefore reducing the capability of neurons to fire at elevated frequencies. This mechanism supplies protections against MES in animals and focal seizures in humans. A low threshold Ca2+ ion current (Type) manages oscillatory comebacks in thalamic neurons. The reduction of current by the use of AEDs such as [(ethosuximide (ESM)], dimethadione, VPA).[26]

Inhibitory neurotransmission: The GABA is the predominant inhibitory NTM in the mammalian CNS and is released at up to 40% of all synapses in the brain. GABA is synthesized from glutamate by the action of the enzyme glutamic acid decarboxylase.

Following release from GABA-ergic nerve terminals, it acts on the post-synaptic GABAA receptor, a ligand-gated ion channel comprising five independent protein subunits arranged around a central chloride ion (Cl-) pore.

The GABA-A receptor responds to GABA binding by increasing Clconductance resulting in fast neuronal hyper-polarization or inhibition. The drug may work directly on the GABA-receptorCl- ion channel complex (e.g., barbiturates, BZDs), and inhibit the metabolism of GABA (e.g., VPA, vigabatrin) or enhance the release of GABA (e.g., gabapentin). This system affords protection against generalized and focal seizures.[27]

Excitatory neurotransmission: Glutamate is the principal excitatory NTM in the mammalian brain. Release from glutama- teergic nerve terminals, it exerts its effects on three specific subtypes of ionotropic receptor in the postsynaptic membrane, designated according to their agonist specificities-AMPA, kainate and NMDA.

These receptors respond to glutamate binding by increasing cation conductance resulting in neuronal depolarization or excitation. The AMPA and kainate receptor subtypes are permeable to Na+ and involved in fast excitatory synaptic transmission. In contrast, the NMDA receptor is permeable to both Na+ and Ca2+, owing to a voltage dependent blockade by Mg2+ at resting membrane potential, is only activated during periods of prolonged depolarization, as might be expected during epileptiform discharges. Metabotropic glutamate

receptors perform a similar function to GABA-B receptors; they are G-protein coupled and act predominantly as auto receptors on glutamatergic terminals, limiting glutamate release. Glutamate is removed from the synapse into nerve terminals and glial cells by a family of specific Na+ -dependent transport proteins and is inactivated by the enzymes glutamine synthetase (glial cells only) and glutamate dehydrogenase. Some AEDs (e.g., PBT, topiramate) block the AMPA receptor and some (Felbamate, remacemide) block NMDA receptors. This vital mechanism has effected in the progress of new AEDs.

Methods of formulation of fast dissolving tablet

1-Disintegrant addition - involves the addition of superdisintegrants in optimum concentration to the formulation to achieve rapid disintegration/dissolution. For e.g. MCC and sodium starch glycolate are used in formulation of efavirenz, crystalline cellulose (AvicelPH-102) and low substituted HPEC used in oxybutinin and pirenzepine formulation. Crosspovidone used in galanthamineHBr. Crosspovidone (3%w/w) and crosscarmellose Na (5%w/w) used in prochlorperazine maleate formulation. Characteristics: similar to conventional tablets with higher % of disintegrants, lower hardness and higher % of friability.

2- Freeze Drying or Lyophilization -the drug is dissolved or dispersed in an aqueous solution of a carrier. The mixture is poured into the wells of the preformed blister packs. The trays holding the blister packs are passed through liquid nitrogen freezing tunnel to freeze the drug solution. Then the frozen blister packs are placed in refrigerated cabinets to continue the freeze drying. Finally the blisters are packaged and shipped. Characteristics: The preparations are highly porous, have high specific surface area, dissolve rapidly and ultimately show improved absorption and bioavailability.

3- Moulding -water-soluble ingredients with a hydro-alcoholic solvent is used and is molded into tablets under pressure lower than that used in conventional tablet compression. Characteristics: Molded tablets are very less compact than compressed tablet porous structure that enhances disintegration/dissolution and finally absorption increased.

4- Sublimation - inert solid ingredients that volatilize rapidly like urea, camphor ammonium carbonate, ammonium bicarbonate and hexamethylenetetramine were added to the other tablet ingredients and the mixture is compressed into tablets. The volatile materials were then removed via sublimation, which generates porous structure. Characteristics: porous structure that enhances dissolution by using volatile material or solvent e.g. cyclohexane, benzene etc.

5-Spray-Drying -by hydrolyzed and non hydrolyzed gelatins as supporting agents, mannitol as bulking agent, sodium starch glycolate or crosscarmellose sodium as disintegrating agent

and an acidic material (e.g. citric acid) and / or alkali material (e.g. Sodium bicarbonate) to enhance disintegration /dissolution. Characteristics: prepared tablet disintegrates within 20 seconds when immersed in an aqueous medium.

6-Mass-Extrusion -involves softening the active blend using the solvent mixture of water soluble polyethylene glycol, methanol and expulsion of softened mass through the extruder or syringe to get a cylindrical shape of the product into even segments using heated blade to form tablets. Characteristics: The dried product can be used to coat granules of bitter tasting drugs and thereby masking their bitter taste.

7- Direct Compression - conventional equipment, commonly available excipients and a limited number of processing steps are involved in direct compression. Characteristics: It is most cost effective tablet manufacturing technique.

8-Cotton candy process - involves the formation of matrix of polysaccharides by simultaneous action of flash melting and spinning. This candy floss matrix is then milled and blended with active ingredients and excipients after re-crystallization and subsequently compressed to FDT. Characteristics: It can accommodate high doses of drug and offers improved mechanical strength.

9- Compaction- Melt granulation b) Phase-transition process - prepared by incorporating a hydrophilic waxy binder (super polystate) PEG-6-stearate. Super polystate not only acts as binder and increase physical resistance of tablet but also helps the disintegration of tablet. Characteristics: It melts in the mouth and solubilizes rapidly leaving no residue. - prepared by compressing a powder containing two sugar alcohols with high and low melting points and subsequent heating at a temperature between their melting points. The tablet hardness was increased after heating process due to increase of inter particle bond induced by phase transition of lower melting point sugar alcohol. Characteristics: The compatibility increased and so sufficient hardness gained by the formulation.

10-Nanonization - involves size reduction of drug to nanosize by milling the drug using a proprietary wet-milling technique. The nanocrystals of the drug are stabilized against agglomeration by surface adsorption on selected stabilizers, which are then incorporated into FDTs. Characteristics: It is used for poorly water soluble drugs. It leads to higher bioavailability and reduction in dose, cost effective manufacturing process, conventional packaging due to exceptional durability and wide range of doses (up to 200 mg of drug per unit).

11- Fast Dissolving Films -a non-aqueous solution is prepared containing water soluble film forming polymer (pullulan, carboxymethylcellulose, hydroxypropyl methylcellulose,

hydroxyl ethyl cellulose, hydroxyl propylcellulose, polyvinyl pyrrolidone, polyvinyl alcohol or sodium alginate, etc.), drug and other taste masking ingredients are used to form a film after evaporation of solvent. In case of a bitter drug, resin adsorbate or coated micro particles of the drug can be incorporated into the film. Characteristics: The thin films size less than 2X2 inches, dissolution in 5 sec, instant drug delivery and flavored after taste.

EVALUATION

Evaluation parameters of tablets mentioned in the Pharmacopoeias need to be assessed, along with some special tests are discussed here.

Weight variation: 20 tablets were selected randomly from the lot and weighted individually to check for weight variation30. Weight variation specification as per I.P. is shown in table 2. weight variation and accepted % deviation Average Weight of Tablet % Deviation 80 mg or less 10.0 More than 80 mg but less than 250 mg 7.5 250 mg or more 5.0.

Hardness: The limit of hardness for the FDT is usually kept in a lower range to facilitate early disintegration in the mouth. The hardness of the tablet may be measured using conventional hardness testers (Monsanto tablet hardness tester). It is expressed in kg or pound.[31]

Friability: To achieve % friability within limits (0.1-0.9%) for an FDT is a challenge for a formulator since all methods of manufacturing of FDT are responsible for increasing the % friability values. Friability of each batch was measure in “Electro lab friabilator. Ten pre-weighed tablets were rotated at 25 rpm for 4 min or total 100 revolutions, the tablets were then reweighed and the percentage of weight loss was calculated by the following equation-

F= W (INITIAL) – W (FINAL)/ W (INITIAL)* 100

Mechanical Strength: Tablets should possess adequate mechanical strength to bear shocks of handling in manufacturing, packaging and shipping. Crushing strength and friability are two important parameters for the determination of mechanical strength. Crushing Strength or Tablet Tensile strength: It is the force required to break a tablet by compression in the radial direction, it is important to note that excessive crushing strength significantly reduces the disintegration time. The crushing strength of the tablet was measured by using Pfizer hardness testers. It is calculated by an average of three observations. Tensile strength for crushing (T) is calculated using equation-

$T= 2F / \pi*d*t$

Where F is the crushing load, and d and t denote the diameter and thickness of the tablet,

Measurement of Tablet Porosity: The mercury penetration porosimeter can be used to measure the tablet porosity. The tablet porosity (ε) can be calculated by using following equation-

$\varepsilon = 1\text{-}m / (\rho t V)$

Where ρt is the true density, and m and V are the weight and volume of the tablet, respect. Wetting time and water absorption ratio: Wetting time of dosage form is related to with the contact angle. Lower wetting time implies a quicker disintegration of the tablet. The disintegration time for FDT needs to be modified as disintegration is required without water, thus the test should mimic disintegration in salivary contents. For this purpose, a petridish (10 cm diameter) was filled with 10 ml of water. The tablet was carefully placed in the center of petridish and the time for the tablet to completely disintegrate into fine particles was noted. The water absorption ratio, R can be the determined according to the following equation-

$R = 100 (Wa\text{-}Wb) / WbWb;$

The weight of the tablet before keeping in the petridishWa; the wetted tablet from the petridish is taken and reweighed.[34]

Moisture uptake studies: Moisture uptake studies for FDT should be conducted to assess the stability of the dosage form. Ten tablets from each formulation were kept in a desiccator over calcium chloride at 370 C for 24h. The tablets were weighed and exposed to 75% relative humidity, at room temperature for 2 weeks. Required humidity was achieved by keeping saturated sodium chloride solution at the bottom of the dessicator for 3 days. One tablet as control (without super disintegrants) was kept to check the moisture uptake by the other excipients. Tablets were weighed and the percentage increase in the weight was recorded.

In-vitro dispersion time: Tablet was added to 10 ml of phosphate buffer solution, pH 6.8 at 37+0.5°c. Time required for complete dispersion of a tablet was measured.

Disintegration test: The time for disintegration of FDTs is generally less than 1 min and actual disintegration time that patient can experience ranges from 5 to 30s. The disintegration test for FDT should mimic disintegration in mouth within saliva.[35]

Modified disintegration test: A petridish (10cm diameter) was filled with 10 ml of water. The tablet was carefully put in the center of petridish and the time for the tablet to completely disintegrate into fine particles was noted.

Disintegration in oral cavity: The time required for complete disintegration of tablets in mouth was obtained from six healthy volunteers, who were given tablets from the optimum formulation.

Dissolution test: The dissolution methods for FDT are practically identical to conventional tablet when FDT does not utilize taste masking. Commonly the drugs may have dissolution conditions as in USP monograph. 0.1N HCl, pH 4.5 and pH 6.8 buffers should be used for evaluation of FDT in the same way as their ordinary tablet counterparts. USP 2 paddle apparatus is most suitable and common choice for dissolution test of FDT tablets as compared to USP1 (basket) apparatus due to specific physical properties of tablets. In paddle apparatus the paddle speed of 25-75 rpm is commonly used. Since the dissolution of FDTs is very fast when using USP monograph conditions hence slower paddle speeds may be utilized to obtain a comparative profile. Large tablets (≥1gram) may produce a mound in the dissolution vessel which can be prevented by using higher paddle speeds.[36]

Clinical studies: In vivo studies show the actual action of FDT in the oral–esophageal tract, their pharmacokinetic and therapeutic efficacy, and acceptability. The investigation using gamma-scintigraphy showed that the dissolution and buccal clearance of fast disintegrating dosage forms was rapid.[37] The esophageal transit time and stomach emptying time were comparable to those of traditional dosage forms i.e. tablets, capsules, or liquid forms.[38]

Stability study (Temperature dependent): The fast dissolving tablets stored under the following conditions for a period as prescribed by ICH guidelines for accelerated studies. (i) 40 ± 1°C (ii) 50 ± 1°C (iii) 37 ±1°C and RH 75% ± 5% The tablets were withdrawn after a period of 15 days and analyzed for physical characterization such as visual defects, Hardness, Friability, Disintegrations, and Dissolution etc. The data obtained is fitted into first order equations to determine the kinetics of degradation

CONCLUSION

Fast dissolving tablets are innovative dosage forms developed and specially designed to overcome some of the problems that seen in conventional solid dosage form i.e. difficulty in

swallowing of the tablet in geriatric and pediatric patients. Fast dissolving tablets are designed to dissolve or disintegrate quickly in the saliva generally within less than 60 seconds (range of 5-60 seconds). Fast dissolving tablets have better patient compliance and acceptance may improve biopharmaceutical properties, bioavailability improved efficacy, convenience, and better safety compared with conventional oral dosage forms. The popularity of FDTs has increased fabulously over the last decade. FDTs need to be formulated for psychotic patients, bedridden, geriatric, pediatric patients, for those patients who may not have access to water, patients who are busy in traveling. FDTs formulations formulated by some of these convetional and patent technologies and FDTs have sufficient mechanical strength, quick disintegration/dissolution in the buccal cavity without water. The newer technologies utilized for the formulation of the FDTs that provide more effective dosage forms with more advantages and minimal disadvantage.

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