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CHEMICAL FORMULATION AND EVALUATION OF RIZATRIPTAN SUBLINGUAL TABLET FOR MIGRAIN

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Abstract -: Migraine is brain disorder and it is headache pain which generally occurs one side of the head various methods of treatment and diagonasis are in progress. There are changes to have a migraine with in myocardial infractions and stroke cases. Migrain an serious in teengers and women The main aims of work to prepare and evalute five different formulation of fast disintegrating tablet by direct compression method of Containing Rizatriptant benzoate using various superdisintegrants like Ergotamine. Accurate quantity of ingredient. The tablet were prepared for pre and post compression studies F3 by using super disintegrants Ergotamine and other ingredient was found to best formulation. The disintegration time is very short in formulation F5(18sec) drug release was completely B Very fast (in18 sec) . Fast disintegrating tablet are suitable dosdosage forms in disease migraine show rapid onset action and quick response/ effect.

Keywords -: Migraine attack , headache , brain pain, sublingual tablet.

Introduction -: Migraine is a general neurological disorder of brain which is reletive to the headach

which is symtoms of numerous health condition .The source of migrain of are able to yet recognise it is

Disease that pain are originated to emerges as a obsevation of chemical activities of sensory which provide intra cranial blood vessels and meaning . Migraine is highly popular in America and obey by the europ where as it is less patients found in Asia and Africa . migraine is specific disease which affects important fraction of world population.Migraine generally seen in adult in the age at their 'teens' and 'twentys' migraine is mostly seen in women then men about 15% women (27milion) and 6% male (10milion) are resulted by migraine in United States Global studies gives that properly 1% world population must have chronic migraine .Migraine is determined by intense throbbing unilateral headache which have symptoms ,- vomiting,nausea pholobia or diarrhoea . migraine can exist by focal neurological phenomenonaura. which is follow they headache know as classical migrain care and
step ,care are the two main importance of migraine Manegment care depend on ceverity of the disease and they their Factor of assisment the neoet important step ' care' in which patients originally simple analogesic but need to progress to move powerfull and effective drug .

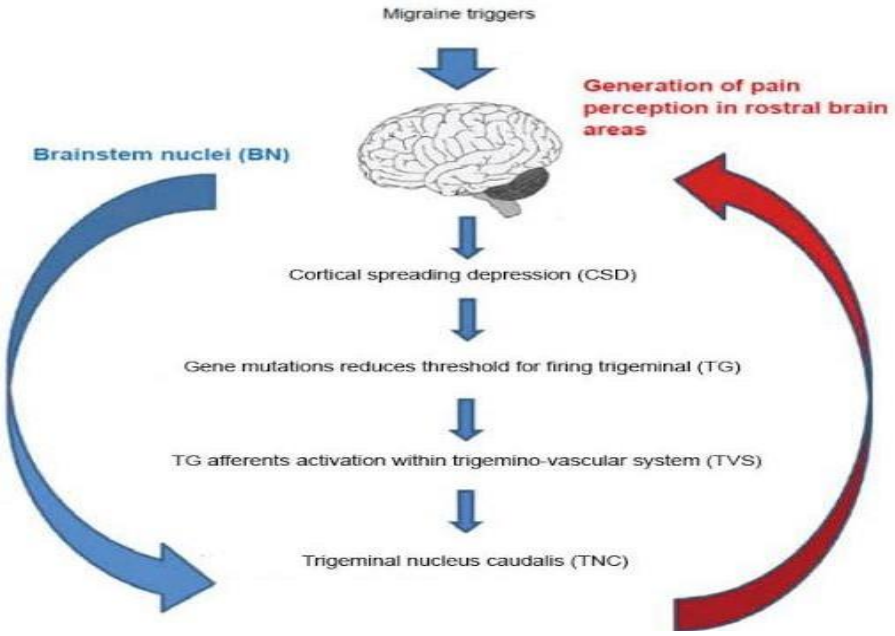

fig no. 1

Pathophysiology-: migraine pain start in the childhood ,or in recent adult, in their teenage migraine candominant into four.Stage -: pro- drome ,postdrome ,aura and headache all stage are accomplished by patients. Patients mayhave experience previous 24-48 hours of a migrain , desirable change can be observed about themigraine are constipation ,change in mood , depression to happiness, neck ,stiffness , increase in urination and thirts .aura occurres in migraine patients know with disirable problem such as zigzag vision ,flash light .That may also attached with touching sensation means motor disturbance.The popularity headache occurres during migraine is different from individuals to adults .in the migrain patient have exp. Pain of throbbing or both side of head , sensitivity of light / sound noice .sometime vometing ,neusea .postdrome is last phase which takes place not before migraine attack. Patients sense elated and some percieve patients also known of confusion ,moodiness diziness and weakness for day.Migraine exposure mostly in sometime in month ,in the course of migrain patient exposureburn pain at one side of head ,nausea , vometing . Postdrome is last stage which one grip later migraine attack .paitient perceive delinghtful andsone patients perceive depleted . paitient to feel like ,anger ,vertigo , mystified and tiredness for 24 hours. All of cause of migrain study that never implicit hence genetics and environmental element orcomponent that motive of migrain or main part that play a important or main part that motive ofmigrain effects the brain stem that motive to pain . migraine also obtain due to interaction between brainstream and trigeminal nerve which is long or big pathway of brain pain serotonin range will be decrease in attack of migrain decrease in serotonin range can due to trigeminal nerve to release some ingredients know as neuropeptide which play towards outer side of brain called meaning . This running of neuropeptide towards the meaninges which results in formation of migraines pain calcitonin gene relased peptide (CGRP) and other are run role in migraine pain .Neurotransmitter and vasoactive substance : substance like nurokinin A , substance p nitric oxide and calcitonin gene- associated with peptide ,which react with blood veins walls and form sterile swelling ,inlargment and protien over vasation are liberate due to perivascular nerve action .This assist in triggering the trigemino cervical complex .This information is then bring in reguarding the cortex and thalomus for the pain.pain in migraine due to neurologically induced plasma over present of other stimulator is need to reason pain as it is insufficient to form pain itself neurogenic plasma extrovasation can be avoid drug which towards migraine.

Migraine center -: Base on results of PET- scan mention tiredable upraised rcbf within brainstem unbroken after resolution of headache form by the sumatriptant and similar analogical sing and symptoms .A potential migraine centre in the brain stem has been formed .The lower rcbf

was not seen outside of attack ,implying that action was not reason by pain consciousness discovering medial motivate for migraine well conssist to be hold better prophylactic agent.

Brain stem Activity -: patient hurt from migrain demonstrates activity of control obliquepons ,underbroken after medificatio may nullity the pain . Trigeminal thalmic system can sensitised in a migrain period .These results revaled that along with preceding mentioned sensitization of middle pathway in brain neuro vascular events starts the pain of migraine .

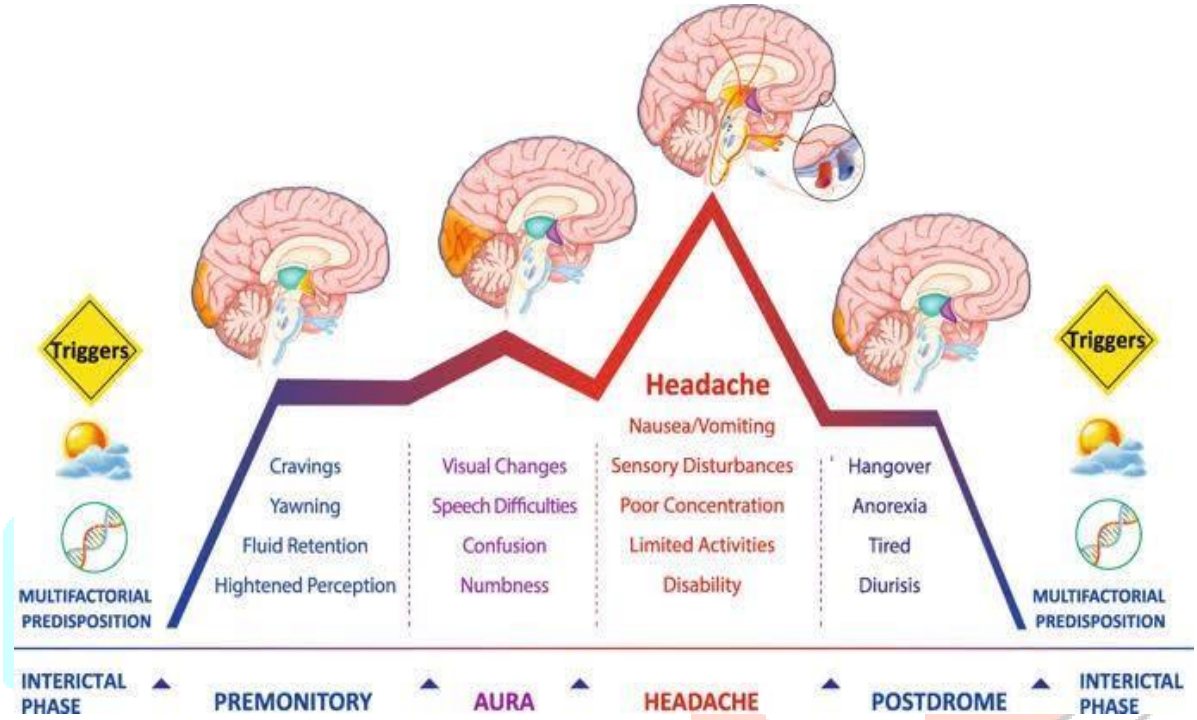

Fig.no.2

Drugs -Amitriptyline Synonyms -;Amitriptylina Disstution time -: 13min

Molecular weight -: 277.4g/mol
Molecularformula-: C20H23N
Dose -: 15-17mg/day

- **Pharmacological Action -**

a) **pharmacodynamic -:** Effect in pain and depressing Amitriptyline is a tricyclic antidepressent and an analgesic. That oral amitriptyline achieves at minimum good to moderate condition Amitriptyline drug use at normal doses for depression. Increase glucose levels can occurs with amitriptyline**.**

b) **Absorbtion -:** rapidly absorbed following oral administration (bioavailability is 30-60% due to 1st pass metabolism) plasma concentrate reached.

c) **Toxicity -:** Toxicity data: increase dose the effects low blood pressure confusion,drowsiness

Use -: Amitriptyline is use for treating pain. To analyse nerve pain (neuralgia) and back pain. To help prevent migraine attack.

2) **Chlorpromazin**
Synonyms :- chlorpromazin, chlorpromazinum
Molecular weight :- 318.86 g/mol
Molecularformula:-C17H19C1N2S
Dissoluation Time -20 min
Dose :- 50mg/day

- **Pharmacological Action:-**

a) **pharmacodinamic -:** chlorpromazin psycholoropic agent indicated for the antiemitic activity chlorpromazine has action at all levels of CNS - primirily at subcortical level as wall as on multiple organ system.

b) **Absorption -:** Readily absorbed from the gastrointestinal tract bioavailability varies due to first- pass metabolism by the liver.

c) **Toxicity -:** Agitation, coma, convulsion, difficulty breathing, difficulty swallowing dry mouth extreme sleepiness, low blood pressure and restlessness.

Use -: used as to treat mood disorders chlorpromazin help to think more clearly , feel less nervous.

3) **Gabapentin**
Synonyms -: Gabapentina **Molecular weight -:** 171.23g/mol
Molecularformula:- C9H18ClNO2
Dissolution time -: 45min
Dose -: 25mg /day

- **Pharmacological Action:-**

a) **pharmacodynamics -:** Gabapentin is an anticonvulsant that inhibits the release of excitatory neurotransmitters allowing for its use against pathologic neurotranmission such as that seen in neuropathic pain.

b) **Absorption -:** Absorption of gabapentin is through to occur solely vio facilitated transport by LATI transpoter within the intestiness. The oral bioavailability of gabapentina is inversaly Proptional to the administered dose the oral bioavailability of 900 mg / day regimen is approximately 60%food has no effect on gabapentin absorption

c) **Toxicity-: multi -** drug overdose involving gabapentin, particularly in combination with other CNS. depressant such opioids. Need of managing overdosage.

Use -: Gabapentin is anticonvulsants [Decrease abnormal excitement in the brain]

4) Ergotamine:-
Synonyms -: ergotaminum

Molecular Weingt = 581.66g/ mol
Molecular Formula = C70H76N10O16
Dissolution time -: 30 min
Dose -: 3-5 mg / day

- **Pharmacological Action -:**

a) Pharmacodynamics -: ergotamine is Vasoconstrictor and α;adrenoreceptor antagonist. The drug has partial against and antagonst activity against tryptaminergic depeending upon theri site and highly active uterine stimulant . It cause construction of peripheral and cranial blood vessels and producess depression of Ceneralvasomotor center. The pain of migraine attack is believed to be due to greatly impulse increase amplitude of pulsation on in cranial arteries, especially the meningeal branches of the external corotide artey Does not reduce cecerebral hemispheric blood flow

b) Absorbtion -: The bioavailability has not determined
C) Toxicity -: signs of overexposure include irritation and confusion
d) Use -: it affectes blood flow patterns that are associated with certain type of headaches and migraine.

5) Rizatriptan
Synonyms = Risatriptan ,Rizatriptán
Molecular Weight = 269.34 g/mil
Molecular Formula = C15H19N5
Dissolution Time = rizatriptan in males and females averages 2-3hours.
Dose -: 5 mg / day

- **Pharmacological Action**

a) Pharmacodynamics = Rizatriptan is a agonst of serotonin (5-HT) type 1B and 1D receptor and this action in humans correlates relief of migraine pain. Rizatriptan equally stimulate 5-HT1 receptors on peripheral terminals of the trigeminal nerve innervating cranial blood vessels, which may equally contribute to the antimigrainous reaction of Rizatriptan in humans.

b) Absorption =. Bioavailability is 45%. Food has no reaction on the bioavailability of rizatriptan. Rizatriptan administering with food will respite by 1 hour the time to reach peak plasma concentration.

c) Toxicity =Symptoms of overdose include dizziness, fainting, heart and blood vessel problems, high blood pressure, loss of bowel, and vomiting.

d) Uses = Rizatriptan is used to treat migraines. It helps to reduce headache, pain, and other migraine symptoms (including nausea, vomiting, sensitivity to light/sound). The certain natural substance

affected (serotonin) that causes narrowing of blood vessels in the brain. It may also reduce pain by affecting certain nerves in the Brain.

5) Magnesium stearate -:

Molecular Weight: 591.2 g/mol **Molecular Formula:** C36H70MgO4 **Synonyms** : Magnesium distearate **Dose -:**
Rizdtpptan = 5mg /day

Amitrypine =15-17mg/day
Gabapentin = 25mg/ day
chlorpromazin = 50 mg /day
Ergotamine = 3- 5 mg / day
Mag. Stearate = 0.5 mg/ day
Method of preparation -:

- Formation of sublingual Tablet by direct compression method -:The sublingual tablet of rizatriptan was prepared by using direct compression method.Accurate compression of all material without magn Magnisum stearate was carried by mesh# 40 and mixed well with other ingredient rizatriptan tablet prepared by passing material mesh # 40 .

- The rizatriptan 5 mg / day, ergotamine 4.5 mg/ day, amitriptyline 15 mg / day,9 gabapentin 25 mg and chlorchlorpromazine 50 mg Erogatamine as the super disintegrent.Mag. Stearate ate with the ergotamine, gabappentin, amitriptyline, chlorpromazin and mixed well. The material was directly compressed by tablet panching machine with concave feed 9 mm of punch and die set. By using direct compression method tablet was formulated.

•Dispensing - Hand out the dispensing of API and excplients in dispensing booth as preparation formula.

- Sifting -filter the API ergotamine, amitripthyline, gabapentin, chlorpromazine, through#40

•Mixing - shift the sifted material in the virgin polynag and mix well.
•Lubrication - sift mag. Stearate through # 80 and shift the lubricating material i.e magnesium stearate in the blend and blend for 300sec.

- Compression - compress the lubricate material in 16 station compression machine by 6.4mm flat punches.

* The pre compression parameters are

1) **Bulk density** - bulk density use to measure the describe packing material. Bulk density is the ratio of mass of powder (given) to it's bulk volume calculated by

Bulk density = W/Vo g/ml.

M =mass of the blend

Vo= untapped volume

2) **Tapped density** = Tap density was the calculated by formula
Tapped density = W/V1g/ml
W= mass of the blend V1
= Tapped volume
3) **Angle of Repse** -: The angle of repose is the angle between surface of pile of blend and the horizontal surface. Angle of repose passing the blengb through funnet fix to burret strand at heigh 14cm . Angle of repose of blend was determine by the formula.

$\theta = \tan^{-1}(h/r)$ h=

height of pile
r = Radius of pile

4) **compressibility** index = on the basis of the appareat bulk density and tapped density the percentage compressibility of the blend was calculated using formula.

% compressibility = [(Tapped density - Bulk density)]×100

5) **Hausners ratio** = It show the flow properties of powder. It is ration of the tapped density to bulk density.

Hausners method = Tapped density / bulk density

Formulation	Bulk density (g/ml)	Tapped density (g/ml)	Angle of repones (Q)	Hausners ratio	compressibility
F1	0.364	0.545	31.5	1.11	10.2
F2	0.379	0.485	29.6	1.2	10.8
F3	0.375	0.530	28.7	1.13	10.6
F4	0.360	0.493	30.2	1.14	10.4
F5	0.375	0.510	29.7	1.9	10.5

- **Post compression parameters are**

- **Hardness test -:** Hardness test of the table was found by the Pfizer hardness teater. The lower player was situated in contact with the tablet and a zero reading talking. The plunger was then forced against a spring by the turning a threaded screw before the table fracture. As the spring was press a pointer runs along a gallge within the barrel to show the force shown in Table 2

- **Thickness -:** The thikness of tablet fast dising egrating tablet was standard by digital vernier calipers. The mean thikness is mentiored in Table -2

- **Friability Test - :** 20 tablets weighed were situated in the appartus which was given 80 revolution and the tablets were reweight. The% friability was measured by using given formula - The results are mentioned in Table 2
Percentage = [(initial wt. - Avrage wt) ÷ initial wt)]×100Friability

- **Disintegration Test -;** tablet disintegration study was presented in disintegration appartus. One tablet in each of the six tubes in a one litre beaker of water, at 87°c+- 2°c.The machine was operated before the tablets were totally disintegrated result were mentioned in Tab. No. 3

- **Drug content -:** for the content uniformality test 10 tablets were weighed and pulverized to a fine powder , a quality of powder equivalent to 12 mg of rizatriptan was transported in a 10 ml std. Flask and the volume was make with mobilie phase further 10ml of the above solution was diluted to 10 ml with mobilie phase result show in table no. 3

- **Wetting time -:** The tablet wetting time was calculated by procedure that is the tablet was situated at the center of two layer of absorbent paper seted into a dish .After that paper was slowly weted with pH 6.9 phosphate buffer was completely out of dish The time for the water to diffuse from the water absorbent paper throughout the entried tablet was then calculated using a stop watch clock. The result mentioned inTable No. 3 and fig no 4

- **Water absorbtion ratio -:** A small part of tissue paper folded twice was situated within a small petri dish contai 6 ml of buffer pH 6.8 . A tablet was put on the tissue paper and allowed to totally wet. The

weted tablet was then weighted water absorbtion ratio, R was calculated by given equation.

The result shown in table no. 3 and fig no. 5 R= 100×
Wa- Wb/Wa
Wa = weight of tablet after water absorbtion
Wb = weight of tablet before water absorbtion. **8)**

In - vitro dissolution studies -: 900 ml of phosphate buffer (pH 6.8) was used as a media and was at the 37 +- to 0.5°c . When the type 2nd USP was set at 50rpm. 5 ml of sample were taken every 2 minutes and the some amount was against placed with fresh buffer. The withdraw sample were cleaned analyzed by using a UV spectrometer at a wavelength of 224nm . The results shown in Table no. 4 and represented in fog.no.6

Ingredients	F1	F2	F3	F4	F5
Rizdtpptan	5	5	5	5	5
Amitrypine	15	16	17	14	16
Gabapentin	25	25	25	25	25
chlorpromazin	50	50	49	50	50
Ergotamine	4.5	3.5	3.5	4.5	3.5
Mag. Stearate	0.5	0.5	0.5	0.5	0.5

- **Table no. 1 Formulation composition of rezatriptan fast disintegrating table.**

Ingredients	Quality for mg table				
	F1	F2	F3	F4	F5
Rizdtpptan	5	6	5	5	5
Amitrypine	15	16	17	14	16
Gabapentin	25	25	25	26	25
chlorpromazin	50	50	49	50	50
Ergotamine	4.5	3.5	3.5	4.5	3.5
Mag. Stearate	0.5	.0.5	0.5	0.5	0.5

- **Table no 2. Evalution of sublingual tablet of rezatriptan**

Formulation code.	Thickness (mm)	Average weight (Mg)	Hardness (Kg/cm²)	Friabilty (%)
F1	2.78 +- 0.2	101.3	2.9	0.6
F2	2.84 +- 0.1	101.50	2.8	0.16
F3	2.91 +- 0.1	101.13	2.7	0.12
F4	2.8 +- 0.2	101.7	2.8	0.14
F5	2.79 +- 9.2	101.6	2.8	0.1

- **Table no.3:- Evalution of sublingual tablet of rezatriptan**

Formulation code	Disintegration time (sec.)	Drug content (%)	Wetting time in (sec.)	Water absobtion ratio (%)
F1	20	99.94	12.1	21.18
F2	17	99.54	11.3	31.24
F3	18	99.91	15.4	34.17
F4	16	99.5	12.5	32.14
F5	15	99.34	13.4	34.37

Table no. 4 Dissolution profile for all formulation in a NHCl dissolution media.

Time in mint.	% Drug Release				
	F1	F2	F3	F4	F5
2	55.18	60.27	67.32	50.78	55.26
4	61.24	72.43	68.34	58.24	60.47
6	68.72	85.24	78.12	64.18	65.47
8	72.47	91.38	98.46	73.18	75. 4
10	80.96	97.75	98.76	77.34	86.58

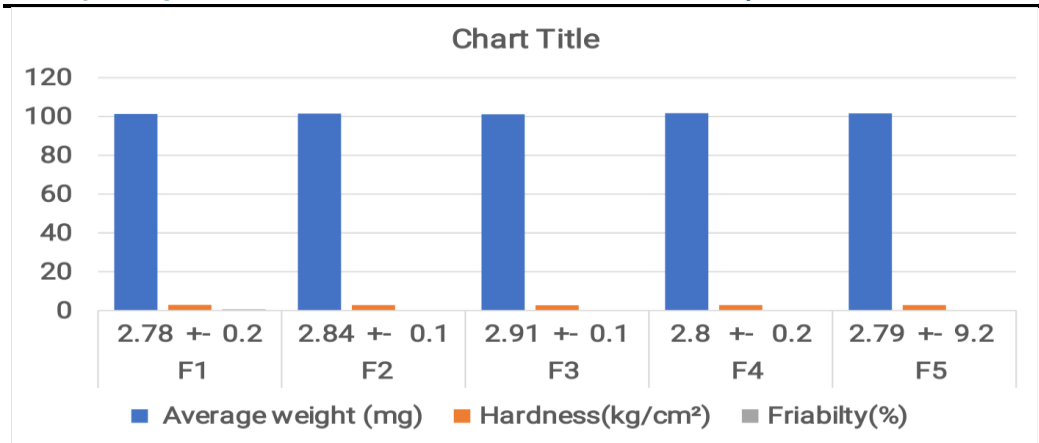

Fig no. 3

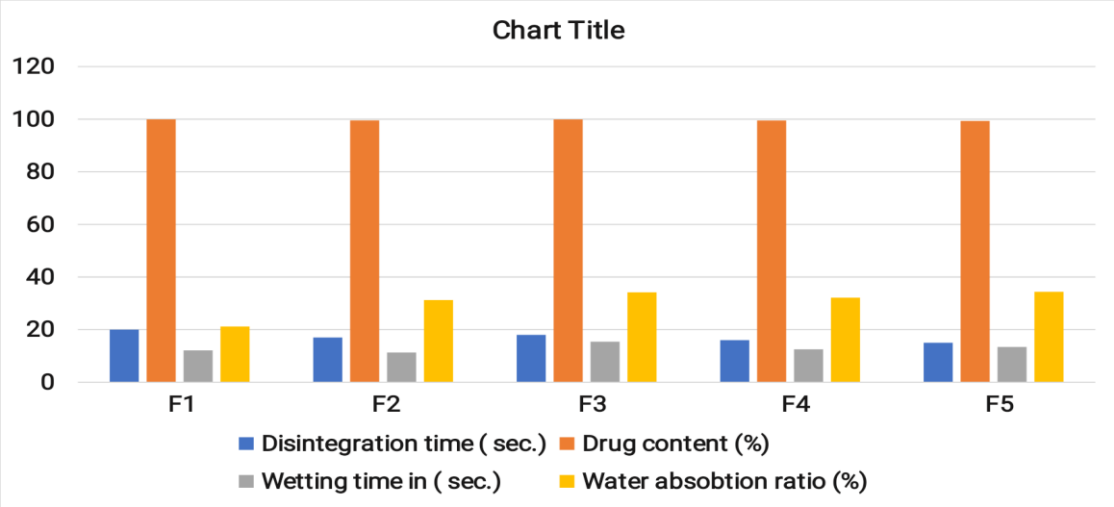

Fig no. 4

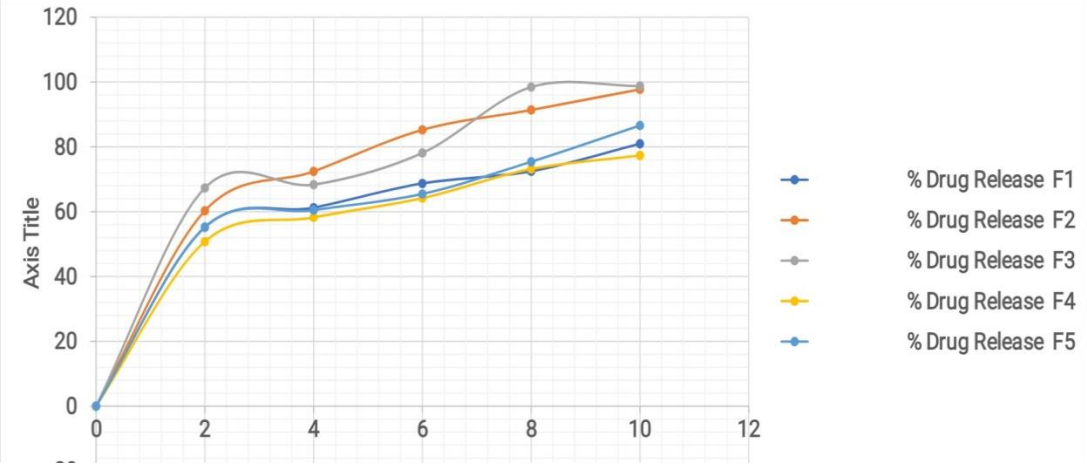

Fig no. 5

Diagnosis -:

sever headache is leads to migraine. The person suffer from migraine has genetic basic, but migraine attack can be triggered by external and internal influences on kids simply come from them for impossible reason.

Diagnosis of migraine is introduced by obtaining by the history from patient. About 20% patient's of migraine have experience of migraine aura generally before headache starts. Pre - symptoms are started from two days before their migraine pain. That includs fatigue, depression, vomiting and some time breathing pain. In pre- monitory phase area of brain gets activated. The increase in above experiences a post drome in which patient experience depression density increase in headache, nausea and fatigue and sensation of light sound, blam and motion. [Physician has criteria and some tests to Digonise migraine.]

Tests for migraine - : Their is no actual specific teat for dignose migraine.

a) MIR (Magnetic resonance imaging) - : MIR (Magnetic resonance imaging) is uses as powerful magnetic field for radio waves to create details picture of brain.

b) C. T. Scan -: CT scan is test which contains α rays and computer are used to produce correct and accurate image of pain of body. A CT scan of head getting the migraine symptoms

c) spinal Tap (lumbarpuncture) -: physician may recommended spinal test if the patients suspect infection, bleeding in brain or other condition.

d) ECG (Electro Encephalography) -: This test involves monitoring the activity of brain by recording impulse generated in the brain.

Result and conclusion -: Fast disintegration table of rizatriptan were formulated and estimated by using disintegrating agent like Ergotamine. The five formulations were formulated estimated for their physical characteristics hardness, thickness, weight variation, fribility, wetting time, absobtion time, disintegration time and established to be in the limits. The result indicate the formulated fast disintegrating table of rizatriptan disply best evalution parameter and fastly disintegrating/ dissolving without the effecting the release profile. On the basis of pre and post compression parameters disintegrating time and dissolution studied F5 formulated by using the super disintegrating agent Ergotamine was better formultion. The dissolving time was very less f5 formulation (in 18 min) when contrast with other prepared formulation fast disintegration table are appropriate dosage from in migraine pain and show rapid action they are quick dissolution dosage from dose depend on patients compliant.

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