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FORMULATION AND IN-VITRO EVALUATION OF SEROTONIN-5HT-1b and SEROTONIN-5HT-1d RECEPTOR AGONIST AGENT-ZOLMITRIPTAN-AN ANTI-MIGRAINE DRUG

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ABSTRACT

Oral drug delivery systems occupy most common route of dosage form administration, of which oral disintegrating tablets plays key significant role in case of minimum time required to get effective therapeutic concentration of a given active pharmaceutical ingredient as ORDs tablets. The selected Zolmitriptan was prepared into oral disintegrating tablets using PRECROL, ACE SULFATE AND CROSSPOVIDONE as major inactive ingredients. FTIR spectra revels that, there is no significant interaction between the pure drug Zolmitriptan and other inactive ingredients used. Total 10 formulation trials were prepared of which trial T-10 was optimized based on the characteristic properties and in-vitro evaluation parameters. Physical evaluation of blends and tablets of all the trials gave optimum range results of angle of repose 23.3 to 28.8, weight variation 97-101, hardness 2.3 to 2.6Kg/Cm^2 and friability was found to be 0.3 to 0.9 percent for all 10 trials. Melt granulation and direct compression techniques were implemented in present work to prepare ORDs tablets, among which trial T-10 tablets prepared by direction compression method were optimized. The % drug release was fitted to various kinetic models to see the release rate of drug form prepared in-house ORDs tablets, and release rate was observed to be KORESMEYER PEPPAS-0.989>FIRST ORDER-0.975>HIGUCHIS PLOT-0.926. The prepared ORDs tablets give immediate therapeutic activity in minimizing migraine.

KEYWORDS: ORDs, oral disintegrating tablets, Zolmitriptan.

INTRODUCTION

Tablets dosage forms which unexpectedly disintegrate inside the mouth and may be taken without water have emerge as extraordinarily famous in current years. Those products offer the convenience of a tablet with the ease of swallowing a liquid. These dosages are of specific benefit in certain patient's in along with kids, elderly, and psychiatric sufferers. Clinical situations which include pain, migraine, nausea, panic attack, allergic conditions, cough or bloodless, and Alzheimer's may benefit from these dosage paperwork. In spite of awesome innovations in drug shipping, the oral course stays the preferred path for administration of therapeutic retailers due to correct dosage, low price therapy, self remedy, non invasive technique and ease of management leading to excessive degree of affected person compliance.[1]

Significance of ODTS[2]

ODTs provide dual advantages of stable dosage bureaucracy and liquid dosage paperwork in conjunction with special capabilities which encompass.

- **Correct dosing:** Being unit stable dosage paperwork, offer luxury of accurate dosing, clean portability and production, excellent bodily and chemical stability and an ideal opportunity for pediatric and geriatric patients.

- **More suitable bioavailability:** Bioavailability of drugs is greater due to absorption from mouth, pharynx and esophagus.

Advantages of ODTS[3]

e• Ease of administration to patients who cannot swallow, which include the aged, stroke sufferers and bedridden sufferers; sufferers who ought to not swallow, inclusive of renal failure sufferers; and who refuse to swallow, along with pediatrics, geriatric and psychiatric patients.

• affected person's compliance for disabled bedridden sufferers and for travelling and busy folks that do no longer have ready access to water.

• excellent mouth sense assets of ODTS enables to alternate the fundamental view of medication as "bitter tablet", in particular for pediatric patients due to advanced taste of bitter pills.

• comfort of management and correct dosing in comparison to liquid formulations.

• Advantage of liquid remedy inside the form of solid practice.

• More fast drug absorption from the pre-gastric location i.e. mouth, pharynx and oesophagus which may produce rapid onset of motion.

• Pregastric absorption can bring about stepped forward bioavailability, reduced dose and improved medical performance by means of lowering side effects.

• New enterprise possibilities: product differentiation, line extension and lifestyles-cycle control, exclusivity of product promotion and patent-existence extension.

Best of ODTs[3]

They should

• Not require water to swallow and ought to dissolve or crumble within the mouth inside some seconds.

• Allow high drug loading.

• Be well matched with flavor masking and other excipients.

• Have a pleasant mouth experience.

• Depart minimum or no residue in the mouth after oral administration.

• Have sufficient electricity to face up to the rigors of the manufacturing method and submit production managing.

• Show off low sensitivity to environmental conditions including humidity and temperature.

• Be adaptable and amenable to current processing and packaging equipment.

• Allow the manufacture of drugs using conventional processing and packaging equipments at low price.

ODTs as a strong dosage form containing medicinal materials which disintegrates swiftly, usually inside a depend of seconds, when placed under the mouth, ODTs are acknowledged by various names inclusive of "rapid-melting, fast-dissolving, mouth melts, mouth dissolving, brief disintegrating, porous tablets, rapimelts or orodispersible tablets."

SUPERDISINTEGRANTS[4]

Disintegrants are substances automatically covered in tablet formulations and in a few tough shell pill formulations to promote moisture penetration and dispersion of the matrix of dosage form in dissolution fluids. An oral solid dosage shape must preferably disperse into the number one particles from which it was organized. Remarkable disintegrants are typically used at a low awareness, generally 1-10% by way of weight relative to general weight of dosage unit. Typically applicable disintegrants are Cross Carmellose Sodium (Ac-Di-Sol), Crosspovidone (Cp), and Sodium starch glycolate (SSG) and so on. Which constitute instance

of cross linked cellulose, cross linked polymer and cross linked starch respectively. Selection of appropriate system excipients and manufacturing generation is important for obtaining the optimized layout capabilities of orally disintegrating dosage bureaucracy. Ideally, super disintegrates should cause the pill to disrupt, now not only into the granules from which it turned into compressed however also into powder particles from which the granules had been prepared.

Choice of Super disintegrants

Even though super disintegrants more often than not affect the charge of disintegration, however when used at high degrees they can also affect mouth feel, tablet hardness and friability. For this reason, numerous perfect elements to be taken into consideration whilst deciding on the right super disintegrants for a particular formulation have to: produce speedy disintegration, whilst pill comes in contact with saliva in the mouth/oral cavity. Be compactable enough to provide much less friable drugs. Produce excellent mouth experience to the patients. As a result, small particle length is favored to reap patient compliance. Have right with the flow, because it improves the float characteristics of total blend.

Mechanism of Movement of Disintegrants

Numerous mechanisms proposed on this challenge encompass water wicking, swelling, deformation restoration, repulsion and heat of wetting. it appears in all likelihood that no single mechanism can give an explanation for the complex conduct of the disintegrants. However, each of those proposed mechanisms offers some understanding of different aspects of disintegrant movement.

Water Wicking[5]

The capacity of disintegrant to draw water into the porous network of tablet is critical for effective disintegration. on preserving the pill into suitable aqueous medium, the medium enters into tablet and replaces the air adsorbed on the debris which weakens the intermolecular bonds and breaks the pill into exceptional debris. Water uptake through tablet relies upon hydrophilicity of the drug/excipients and on tableting situations. In contrast to swelling, which is mainly a measure of quantity expansion with accompanying force generation, water wicking isn't necessarily accompanied by a quantity growth. The potential of a system to draw water may be summarized by using Washburn’s Equation.

$$L2 = (\Gamma \cos\theta/2\eta) \times Rt$$

The Washburn equation is just too simplistic to use to a dynamic tablet-disintegration manner, however it does display that any trade in the surface anxiety (γ), pore length (r), strong-liquid touch perspective (θ) or liquid viscosity (η) could change the water wicking performance. l is the period of water penetration inside the capillary and t is the time. This technique is also considered as capillary action approach.

Swelling

Even though water penetration is a essential first step for disintegration, swelling might be the maximum broadly typical mechanism of movement for tablet disintegrants. For swelling to be effective as a mechanism of disintegration, there ought to be a superstructure against which disintegrant swells.

Discern represents the disintegration of pill by wicking and swelling. Swelling of the disintegrant in opposition to the matrix ends in development of a swelling pressure. A big inner porosity within the dosage form wherein a whole lot of the swelling may be accommodated reduces the effectiveness of the disintegrant. Then again, sufficient swelling force is exerted inside the pill with low porosity. It's far worthwhile to note that if packing fraction may be very high, fluid is not able to penetrate in the pill and disintegration is once more slowed down.

Warmth of Wetting[6]

When disintegrants with exothermic houses get wetted, localized stress is created because of capillary air expansion, which aids in disintegration of pill. This rationalization, however, is confined to only some sorts of disintegrants and cannot describe the action of most cutting-edge disintegrating agents.

Wicking: Disintegrant draws water into the Particles swell and break up the pores and reduces the physical matrix.

Swelling: swelling sets up; Bonding forces between particles. Localized stress spreads through-out the matrix.

Disintegration of table via wicking and swelling Due to Release of gases Carbon dioxide gets released inside capsules on wetting because of interplay among bicarbonate and carbonate with citric acid or tartaric acid. The pill disintegrates due to era of stress inside the tablet. This bubbling mixture is use very rapidly dissolving drugs or speedy disintegrating pill. As

those disintegrants are fairly touchy to small modifications in humidity stage and temperature, strict manage of environment is required throughout guidance of the capsules. The bubbling combo is both introduced immediately prior to compression or can be brought into separate fractions of formulation.

Particle repulsive forces[7]

That is every other mechanism of disintegration that attempts to provide an explanation for the swelling of pill made with non-swellable disintegrants. Guyot-Hermann proposed a particle-particle repulsion idea to give an explanation for the remark that debris which do now not swell drastically along with starch, ought to nonetheless disintegrants tablets. In step with this idea, water penetrates into tablet thru hydrophilic pores and a non-stop starch network is created that could convey water from one particle to the following, providing a enormous hydrostatic stress. The water then penetrates between starch grains due to its affinity for starch surfaces, thereby breaking hydrogen bonds and different forces keeping the pill collectively. The electric repulsive forces among particles are the mechanism of disintegration and water is needed for it.

Deformation healing

Deformation restoration principle implies that the form of disintegrant debris is distorted during compression and the debris return to their precompression shape upon wetting, thereby causing the tablet to break apart. This kind of phenomenon can be an crucial factor of the mechanism of motion of disintegrants inclusive of crospovidone and starch that showcase little or no swelling. Disintegration of pill by using deformation in addition to repulsion is illustrated in figure

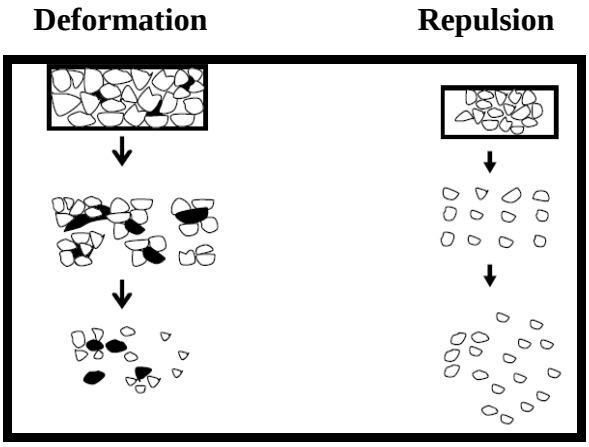

Figure no 01: process of disintegration of tablets.

Particles swell to pre-compression

Water is drawn into the pores and size and break up the matrix particles repel each other due to the resulting electrical force.

Disintegration by deformation and repulsion by enzymatic response.

Enzymes present inside the body also act as disintegrants. Those enzymes dearth the binding movement of binder and allows in disintegration. Due to swelling, pressure is exerted within the outer route that reasons the tablet to burst or the improved absorption of water ends in significant boom inside the quantity of granules to sell disintegration.

Selection of drug applicants for ODTs[8]

Numerous factors should be considered at the same time as deciding on the suitable drug candidate for improvement of orally disintegrating dosage forms. The last traits of a drug for dissolution within the mouth and pregastric absorption from ODTs include.

- Loose from sour flavor.
- Dose decrease than 20 mg.
- Small to mild molecular weight.
- Precise solubility in water and saliva.
- Partly un-ionized on the oral cavity's pH.
- Capacity to diffuse and partition into the epithelium of the top GIT (log P >1, or ideally >2).
- Capacity to permeate oral mucosal tissue. In evaluation, the following traits can also render a drug incorrect for delivery as an orally disintegrating dosage shape:
- Short 1/2-existence and common dosing.
- Very bitter or in any other case unacceptable taste because flavor overlaying cannot be efficiently executed.

Table no 01: Description of disintegrants used in pharmaceutical industries.[9]

Popular Disintegrants used in tablets	Mechanism
Starch	Disintegrate forms pathways throughout the tablet matrix that enable water to draw into the structure by capillary action thus leading to disruption of tablet.
Pregelatinized starch	Responsible for increased dissolution rate from this tablet is rapid disintegration due to superior swelling capacity.
Sodium Starch Glycolate	Involves rapid absorption of water leading to an enormous increase in volume of granules result in rapid and uniform disintegration.
Cross-linked polyvinyl Pyrrolidone	The capillary activity of cross povidone for water is responsible for its tablet disintegration property.
Cellulose	They show their ability to swell on contact with water results in rapid tablet disintegration.
Microcrystalline Cellulose	Allowing water to enter the tablet matrix by means of capillary pores, which break the hydrogen bonding between adjacent bundles of cellulose microcrystals and exhibit very good disintegrant property
Alginates	High affinity for water absorption and high sorption capacity make it an excellent disintegrant.
International Journal of Pharmaceutical Sciences and Research ISSN: 0975-8232 Available online on www.ijpsr.com 24 Soy polysaccharides	Natural super disintegrant, Rapid swelling in aqueous medium or wicking action. Does not contain any starch or sugar. Used in nutritional products.
L-HPC	Both swelling and wicking
Gums	As disintegrants because of their tendency to swell in water
Chitin and Chitosan	Moisture sorption and water uptake was found the major mechanism of disintegration while dissolution related to swelling capacity
Smecta	Their layered leaves like structure consist of aluminium and octahydral layers sandwiched between two tetrahydral silica layers. It has a large specific area and high affinity for water makes it good disintegrant.
Isapghula Husk	Plantagoovata seeds husk has high swellability and gives uniform and rapid disintegration.
Polacrillin Potassium	It swells up at very fast rate upon contact with water or gastro intestinal fluid and act as an effective tablet disintegrant
Ion Exchange Resins	Resins have ability to swell in the presence of water, showed disintegration of tablet.
Gas – Evolving disintegrants	These react in contact with water to liberate carbon dioxide that disrupts the tablet

MATERIALS AND METHODS

Active pharmaceutical ingredient ZOLMITRIPTAN was collected as a gift sample form Intas Pharma and other inactive ingredients were purchase locally from SD Fine Chemicals, Hyderabad.

Formulation of ZOLMITRIPTAN oral disintegrating tablets

In this present research work oral disintegrating tablet were prepared by wet granulation technique and direct compression method.

Formulation of oral disintegrating tablets by melt granulation technique.

Table no 03: ingredients used in formulation of Zolmitriptan tablets trial T-01 to T-05.

S. NO	INGREDIENTS	T-2	T-2	T-3	T-4	T-5
1	ZOLMITRIPTAN	10	10	10	10	10
2	SORBITOL	20	10	7.5	15	15
3	PEG6000	3	1.5	1.12	2.25	2.25
4	PRECIROL	0	0	0	0	0
5	AEROSIL	1	1	1	1	1
6	MANNITOL	56.3	67.8	70.63	62	59.3
7	CROSSPOVIDONE	7.5	7.5	7.5	7.5	10
8	PIPPERMINT	0.25	0.25	0.25	0.25	0.25
9	MAGNESIUM STEARATE	0.5	0.5	0.5	0.5	0.5
10	ACE SULFATE PT	1.5	1.5	1.5	1.5	1.5
	TOTAL WEIGHT OF TABLET IN MG	100	100	100	100	99.8

Formulation of oral disintegrating tablets by Direct Compression technique.

Table no 04: ingredients used in formulation of Zolmitriptan tablets T-06 to T-10.

SNO	DIRECTCOMPRESSION	F6	F7	F8	F9	F10
1	ZOLMITRIPTAN	10	10	10	10	10
2	PRECIROL	5	7.5	10	15	7.5
3	AEROSIL	1	1	1	1	1
4	MANNITOL	74.25	71.75	69.25	64.25	69.25
5	CROSSPOVIDONE	7.5	7.5	7.5	7.5	10
6	ACE SULFATE PT	1.5	1.5	1.5	1.5	1.5
7	PIPPERMINT	0.25	0.25	0.25	0.25	0.25
8	MAGNESIUM STEARATE	0.5	0.5	0.5	0.5	0.5
	TOTAL WT(mg)	100	100	100	100	100

Preparation of oral disintegrating tablets by melt granulation method:

Melt granulation approach is a manner by which pharmaceutical powders are efficaciously agglomerated via a soften capable binder. The advantage of this method compared to a conventional granulation is that no water or natural solvents is needed. For accomplishing this manner, high shear mixers are applied, wherein the product temperature is raised above the melting factor of binder with the aid of a heating jacket or by way of the warmth of friction generated by means of impeller blades. This technique to prepare FDT with enough mechanical integrity, includes the usage of a hydrophilic waxy binder (Superpolystate©, PEG-6-stearate). Superpolystate© is a waxy cloth with a melting factor of 33–37°C and a HLB cost of nine. So it wills no longer simplest act as a binder and increase the bodily resistance of tablets however will also help the disintegration of the tablets as it melts in the mouth and solubilized unexpectedly leaving no residues.

Preparation of oral disintegrating tablets using direct compression method

Drug and excipients were allowed to pass through 40 # mesh one after the other and then switch it to poly bag and mix it for three minutes.

Upload other excipients to the above aggregate al last upload the Glidant (Magnesium Stearate) to the above combination mix it for 2min.

Compress the above lubricated combo by using 7mm spherical punches.

Preformulation Studies

A. Color, Odor, Flavor

The drug pattern changed into evaluated for its coloration and odor. The outcomes are shown in desk.

B. Melting point willpower

Melting factor of the drug sample was determined through capillary technique by using the use of melting factor equipment.

C. **Determination of Solubility**

The solubility of the Zolmitriptan become decided by using including excess quantity of drug in the solvent and equilibrium solubility changed into determined via taking supernatant and studying it on Perkin Elmer Lambda35, double beam spectrophotometer.

D. Ultraviolet seen (UV-visible) spectroscopy

Determination of Calibration Curve

Preparation of stock solution

As it should be weighed a hundred mg of Zolmitriptan changed into dissolved in one hundred ml of (1.2pH 0.1N HCl). The consequent answers have been having concentration of thousand µg/ml (1.0 mg/ml). 10 ml of this solution become similarly diluted as much as 100.zero ml with buffer and to provide an answer of Concentrations one hundred µg/ml. This resultant answer is used as running stock answer for similarly look at. Similarly dilutions were organized from the identical answer.

Serial dilutions

Suitable aliquots have been pipette out from the usual inventory answer in to a chain of 10 ml volumetric flasks. The quantity was made on top of things with buffer to get a set of solutions having the attention variety of 2, 3, 4, 5, and 6µg/ml for Zolmitriptan. Absorbances of the above solutions had been measured at 225 nm and a calibration curve of absorbance against concentration was plotted and the drug follows the Beer's & Lambert's law in the concentration range of 2-6 µg/ml. The regression equation and correlation coefficient changed into decided.

Bulk density, Tapped density, % Compressibility index & Hausner's ratio

Bulk Density

The bulk density was determined by moving the accurately weighed pattern of powder to the graduated measuring cylinder. The initial volume and weight turned into cited. Ratio of weight of the sample was calculated by the use of the following formula.

Density = Mass/quantity

Tapped Density

Weighed powder sample was transferred to a graduated cylinder and become located on the faucet density apparatus, changed into operated for fixed variety of taps (200). The tapped density became determined through the following method.

Density = Mass/Tapped extent

Percentage Compressibility (or) Carr's index (%)

Based totally on the obvious bulk density and the tapped density, the proportion Compressibility of the bulk drug became decided via the subsequent formulation.

Carr's index (%) = [(Tapped Density-Bulk Density) / Tapped Density] X one hundred.

Table no 05: Compressibility limits with respective flow.

S.No	%Compressibility	Flow ability
1	12-May	Excellent
2	16-Dec	Good
3	18-21	Fair
4	23-25	Poor
5	33-38	Very poor
6	More than	Discarded

Assessment of Tablets

The quantitative evaluation and evaluation of a capsules chemical, physical and bioavailability houses are critical within the layout of tablets and to monitor product exceptional. There are various standards that have been set within the various pharmacopoeias regarding the first-rate of pharmaceutical drugs. Those encompass the diameter, length, form, thickness, weight, hardness, Friability and in-vitro-dissolution characters.

Physical characteristic

The general look of a pill, its identification and general elegance is essential for consumer attractiveness, for manipulate of lot-to-lot uniformity and tablet-to-pill uniformity. The fashionable appearance entails the dimension of length, shape, color, presence or absence of odour, taste etc.

Size & shape

It is able to be dimensionally described & managed. The thickness of a pill is best variables. Tablet thickness can be measured via micro-meter or by different tool. Tablet thickness need to be managed within a ± 5% variation of trendy value.

Weight variant

that is an in system first-rate control take a look at to make sure that the manufacturers manage the version in the weight of the compressed tablets, extraordinary pharmacopoeia specify those weight variant assessments These assessments are based at the comparison of the weight of the man or woman capsules (xi) of a pattern of drugs with an top and decrease percent restriction of the discovered pattern common (x-mean). The USP has supplied limits for the common weight of uncoated compressed capsules. Those are relevant whilst the tablet

includes 50mg or greater of the drug substance or while the latter accommodates 50% or extra, via weight of the dosage shape.

METHOD

Twenty tablets have been weighed individually and the common weight became calculated. The individual tablet weights are then compared to the average weight. No longer greater than two pills have to vary in their average weight with the aid of more than percentages said in USP. No tablet need to differ through extra than double the relevant percent.

Table no 06: Percent of limits permitted in weight variation.

Average weight of tablet (mg)	% Difference allowed
130 or less	10%
From 130 to 324	7.50%
> 324	5%

Content uniformity

The drug content of the oral dispersible pills become determined by standards and it meets the necessities if the quantity of the active factor in each of 10 examined tablets lies in the variety of 90% to 110% of the same old amount.

Ten tablets were weighed and brought into a mortar and beaten into pleasant powder. An as it should be weighed portion of the powder equivalent to about 10mg of became transferred to 100ml volumetric flask containing 70ml of zero.1N Hcl buffer. It becomes shaken by means of mechanical approach for 1hr then it was filtered thru Watsmann clear out paper (no.1) and diluted to 100ml with 0.1NHcl buffer. From this resulted solution 1ml became taken, diluted to 50ml with 0.1N HCL buffer and absorbance changed into measured against blank at 225 nm.

Friability

Friction and surprise are the forces that most usually cause capsules to chip, cap or destroy. The friability check is closely related to pill hardness and designed to assess the capacity of the pill to withstand abrasion in packaging, handling and delivery. It’s also measured by way of the use of the Roche friabilator.

Technique

Some of drugs are weighed and located in the apparatus in which they may be uncovered to rolling and repeated shocks as they fall 6 inches in every flip in the equipment. After 4 mins of this remedy or a hundred revolutions, the tablets are weighed and the burden in comparison with the preliminary weight. The loss because of abrasion is a degree of the pill friability. The price is expressed as a percent. A maximum weight reduction of no longer extra than 1% of the burden of the capsules being examined for the duration of the friability test is considered commonly suited and any damaged or smashed capsules are not picked.

The percentage friability changed into decided by way of the formulation.

% friability = (W1-W2) / W1 X 100

W1 = Weight of tablets before test

W2 = Weight of tablets after test.

In-vitro Drug Release Studies

In vitro drug launch become studied the usage of USP II equipment, with 900 ml of dissolution medium maintained at 37±1°C for 45 mnts, at 50 rpm. 0.1 N HCl (pH 1.2) became used as a dissolution medium for the first 5mnts, accompanied by using pH 0.1N HCL buffers for similarly 45mnts. 5ml of sample changed into withdrawn in distinctive time intervals, and became changed by an identical volume of sparkling dissolution medium of equal pH. Gathered samples had been analyzed spectrophotometrically at 225 nm, and cumulative percent drug release turned into calculated. The observed turned into executed in triplicate.

Determination of release rate kinetics

If you want to describe the DS release kinetics from individual pill formulations, the corresponding dissolution facts were equipped in diverse kinetic dissolution fashions:

Order, first order, and Higuchi respectively.

$Qt = Q0 + K0_t$

Where, Qt is the amount of drug launched at time t; Q0 the quantity of drug in the solution at t = zero, (normally, Q0 = zero) and K0 the zero order launch regular.

logQt = logQα+ (K1 /2.303) t

Qα being the total amount of drug within the matrix and K1 the primary order kinetic consistent.

Qt = KH. t ½

Wherein, KH is the Higuchi rate constant.

Further, to higher characterize the mechanism of drug release from matrices, dissolution information had been analyzed the use of the equation proposed by means of Koresmeyer and Peppas.

$Q (t-l) /Q\alpha = KK (t-l) n$

Where, Qt corresponds to the quantity of drug released in time t, l is the lag time (l = 2 hours), Qα is the full quantity of drug that ought to be launched at countless time, KK a constant comprising the structural and geometric characteristics of the tablet, and n is the discharge exponent indicating the kind of drug release mechanism. To the determination of the exponent n, the points in the launch curves where Q (t-l)/Qα>zero.6, had been simplest used. If n approaches to 0.five, the release mechanism can be Fickian. If n tactics to one, the discharge mechanism can be zero order and then again if zero.5<n<1, non-Fickian (anomalous) transport could be received. Anomalous (non-Fickian) shipping generally refers back to the drug launch by way of the summation of each diffusion and erosion of the polymeric matrix. The standards employed to choose the ‘‘fine version’’ changed into the one with the very best coefficient of dedication (r2).

Stability Studies

According to ICH guide lines, the prepared in-house oral disintegrating tablets were subjected to one month stability studies at specified temperature and humidity conditions.

1. 25^0C/60% RH analyzed every month for length of 1 month.
2. 30^0C/seventy five% RH analyzed each month for duration of 1 month.
3. 40^0C/75% RH analyzed each month for duration of 1 month.

RESULTS AND DISCUSSION

Results of methodology are described accordingly.

Preformulation studies of API.

API CHARACTERIZATION

Table no 07: Physical Properties of API.

S.NO	API CHARACTERISATION	RESULTS
1	Physical Appearance	yellow powder
2	Melting point	135^{o}C
3	Solubility	Methanol, water
4	Bulk density	0.23GM/ML
5	Tapped Density	0.493GM/ML
6	Carr's index	17.32
7	Hausner's Ratio	1.93

The value of API compressibility index is 17.23%, 15-25%, less than 15% indicates poor flow ability, optimum flow ability and high flow ability respectively.

Table no 08: Micrometrics Properties of final blend of trial-01 to trial T-05.

Parameter	F1	F2	F3	F4	F5
Angle of repose	27^{0}55	29^{o}39	23^{o}.3	28^{0}8	28^{0}65
Bulk density	0.63	0.55	0.51	0.47	0.6
Tapped density	0.66	0.63	0.54	0.52	0.64
Cars index	4.76	14.54	5.88	10.6	6.66
Hausner's ratio	1.047	1.14	1.05	1.1	1.06

Table no 09: Micrometrics Properties of final blend of trial-06 to trial T-09.

Parameter	F6	F7	F8	F9
Angle of repose	26^{0}74'	28^{o}39	21^{0}81	24^{0}81
Bulk density	0.57	0.46	0.42	0.61
Tapped density	0.63	0.51	0.53	0.69
%Compressibility	10.52	10.86	26.19	13.11
Hausner's ratio	1.1	1.1	1.15	1.13

Calibration of Zolmitriptan

Standard graph of Zolmitriptan in0.1N HCl (pH buffer).

The construction of normal activity curve of Zolmitriptan was done by mistreatment zero.1N HCl as the medium. Zolmitriptan was found to possess the most absorbance at 225 nm. The standard graph of Zolmitriptan in 0.1N HCl was created by creating the concentrations of 2µg/ml, 3µg/ml, 4 µg/ml, five µg/ml and six µg/ml solutions. The absorbance of solutions was examined below UV- photometer at Associate in Nursing absorption most of 225 nm. The quality graph of Zolmitriptan was created by taking the absorbance on coordinate axis and concentrations on coordinate axis.

Table no 10: Concentrations for calibration curve.

S.	CONCENTRATION(µg/ml)	ABSORBANCE
1	0	0
2	2	0.221
3	3	0.321
4	4	0.415
5	5	0.535
6	6	0.624

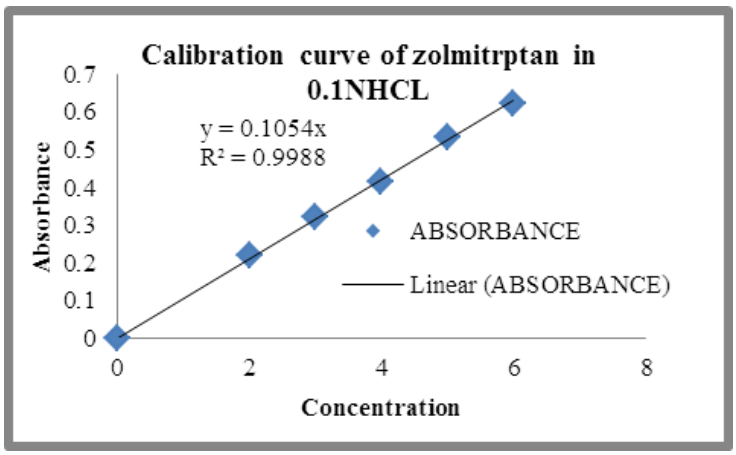

Figure no 02: Graphical representation of calibration curve.

Fourier Transformation Infra-red (FTIR) analysis

Infra-red spectroscopy analysis was performed by Fourier Transformation Infrared Spectrophotometer Alpha Brooker FTIR (Tokyo, Japan).The instrument was calibrated by using polystyrene film.

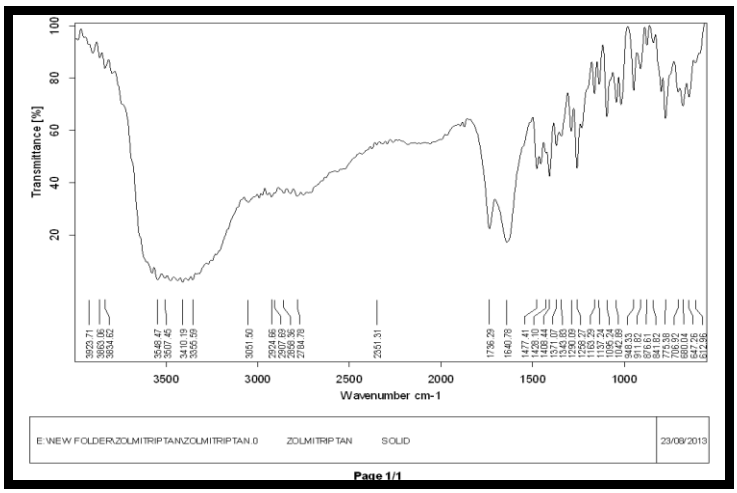

Figure no 03: FTIR Spectra Pure Zolmitriptan.

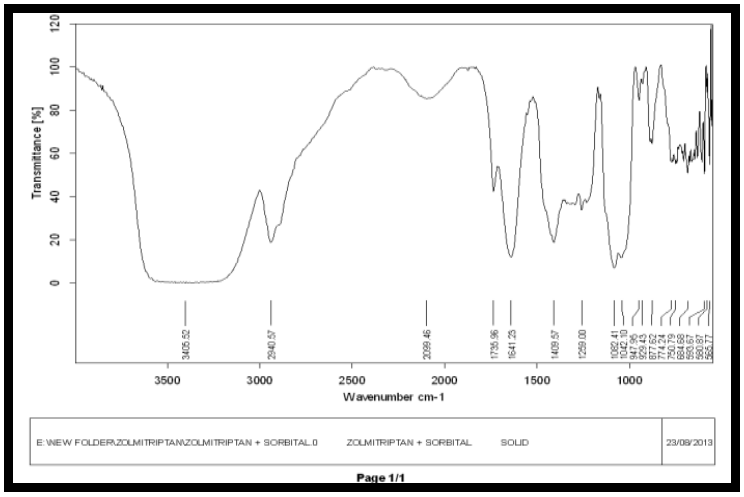

Figure no 04: FTIR spectra of Zolmitriptan with Sorbital.

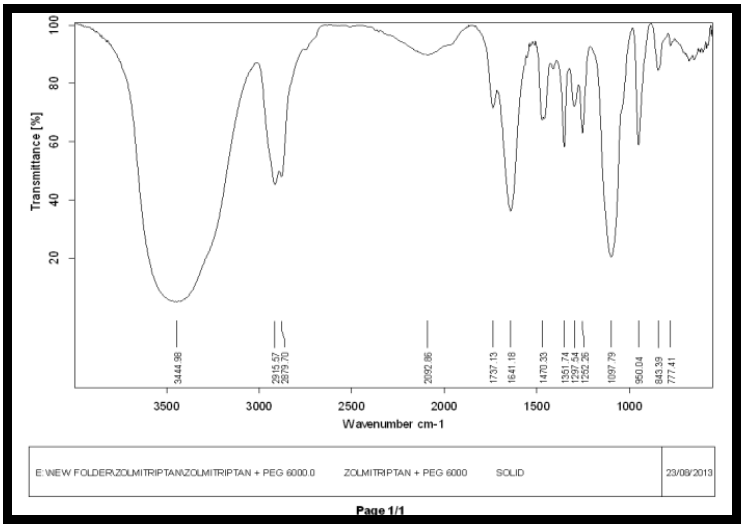

Figure no 05: FTIR spectra of Zolmitriptan with PEG-6000.

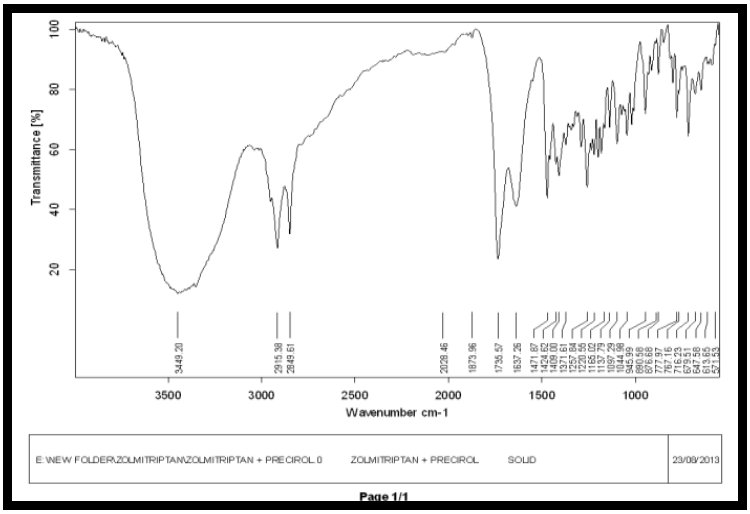

Figure No 07: Ftir For Zolmitriptan And Precirol.

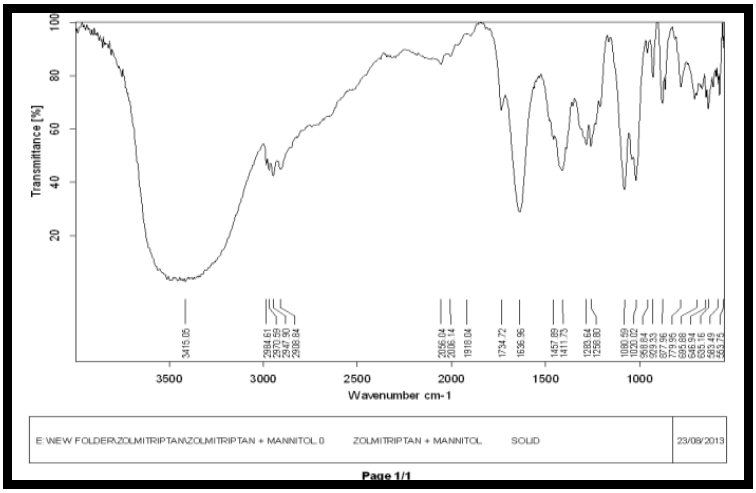

Figure No 08: Ftir Zolmitriptan Mannitol.

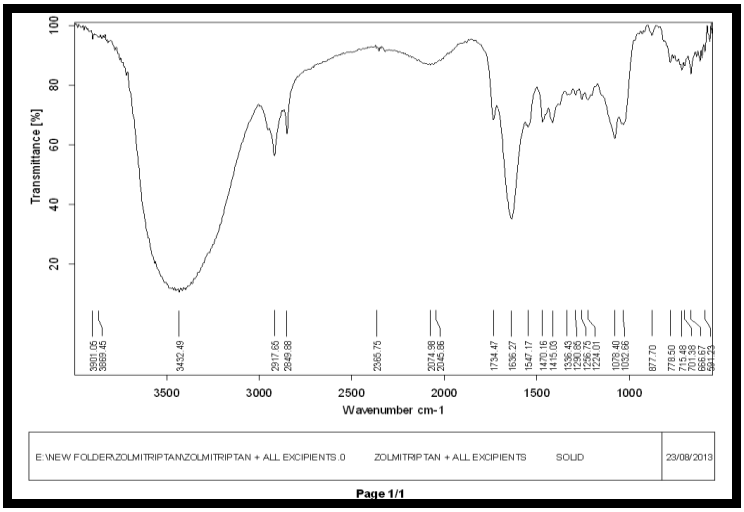

Figure No 09: Ftir Zolmitriptan All Excipients.

FTIR spectra of the data given above graphs give us the clear picture that there is no much interaction between the pure Zolmitriptan and other inactive ingredients.

Evaluation parameters of in-house prepared tablets.

Table no 11: In-vitro evaluation parameters from T-01 to T-05

Parameter	F1	F2	F3	F4	F5
Weight variation	97	99	97	98	98
Thickness (mm)	15	15.7	23	26.5	29
Hardness (kg/cm^2)	2.4	2.3	2.5	2.3	2.4
Friability(%W/W)	0.3	0.35	0.4	0.3	0.4
Content uniformity (%)	98	98.4	98.6	98.8	99

Table no 12: In-vitro evaluation parameters from T-06 to T-10.

Parameter	F6	F7	F8	F9	F10
Weight variation	101	100	99	101	101
Thickness (mm)	34	32	41	41	42
Hardness (kg/cm^2)	2.5	2.3	2.6	2.5	2.5
Friability(%W/W)	0.5	0.6	0.8	0.9	0.9
Content uniformity (%)	99.17	99	99	99.68	100

In-vitro drug release studies

Release of Zolmitriptan was observed in 0.1N HCL at regular intervals, the percent of drug release of Zolmitriptan from in-house prepared tablets are given in below table.

Table no 13: Drug release from trial T-01 to T-05.

TIME	T-1	T-2	T-3	T-4	T-5
0	0	0	0	0	0
5	5.34	10	8.12	2.98	12.12
10	40.25	15.34	14.28	39.22	28.23
15	44.37	23.45	21.82	35.68	34.23
20	68.34	49	34.23	36.72	54.23
30	87.34	23	42.45	39.62	76.93
40	90.12	34.76	54.23	55.07	88.83
50	93.28	83.25	71.23	59.36	97.34
60	95.24	98.83	88.39	98.23	99.3

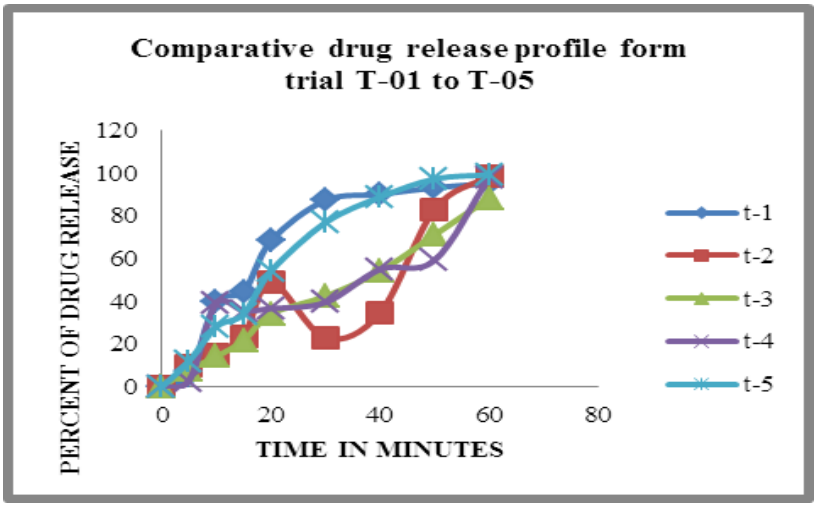

Figure no 10: Graphical representation of drug release from trial T-01 to T-05.

Table no 14: Drug release from Trial T-05 to T-10.

TIME	T-6	T-7	T-8	T-09	T-10
0	0	0	0	0	0
5	10.23	10.23	6.39	5.23	8.23
10	18.36	20.34	12.84	9.26	20.43
15	23.56	32.56	35.83	16.28	35.29
20	56.04	75.35	55.38	21.74	50.12
30	75.45	88.49	64.34	35.39	65.18
40	86.45	93.24	68.83	49.38	72.85
50	92.45	95.78	78.38	64.98	84.29
60	99.56	99.34	93.45	76.28	98.38

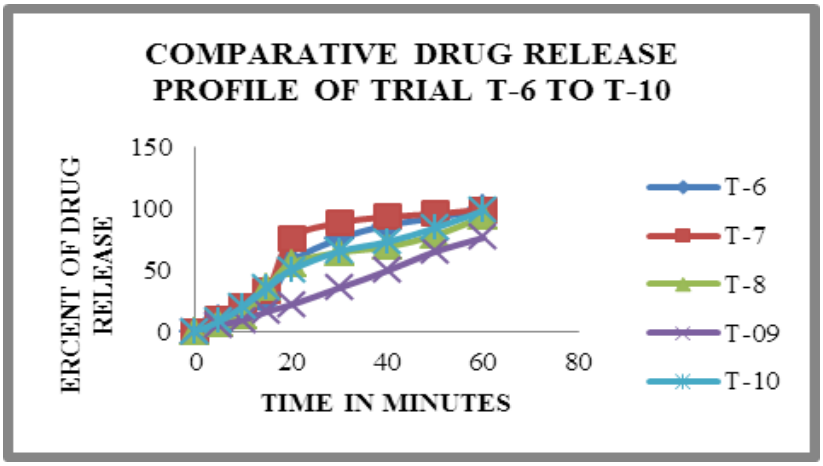

Figure no 11: Graphical representation of drug release from trial T-06 to T-10.

OPTIMIZATION AND REPRODUCIBLE BATCH TRIAL T-10

TRIAL T-10 was optimized based on the drug release and other in-vitro evaluation parameters and was taken for stability studies for one month accelerated conditions 60^{o}C, 60% RH.

Table no 15: Physical characteristics of tablet after one month stability studies at accelerated condition.

Parameter	T-10
Weight variation	98
Thickness (mm)	17
Hardness (kg/cm^2)	2
Friability(%W/W)	0.4
Content uniformity (%)	99

IN-VITRO DRUG RELEASE STUDIES AFTER ONE MONTH STABILITY STUDIES

Table no 16: Drug release studies after one month accelerated stability studies.

TIME	T-10
0	0
5	6.4
10	15.39
15	24.94
20	45.93
30	67.83
40	78.33
50	86.93
60	99.73

DETERMINATION OF RELEASE RATE KINETICS

Table no 17: Data of Release rate kinetics.

ZERO ORDER		FIRST ORDER		HIGUCHIS PLOT		KORESMEYER PEPPAS PLOT	
TIME IN MINUTES	% DRUG UN DISSOLVED	TIME IN MINUTES	LOG 100-Q	SQ TIME	% MEAN DISSOLVED	LOG TIME	LOG CUMMULATIVE % DRUG DISSOLVED
0	0	0	0	0	0	0	0
5	93.6	5	1.97	2.24	6.4	0.7	0.81
10	84.6	10	1.93	3.16	15.39	1	1.19
15	75.1	15	1.88	3.87	24.94	1.18	1.4
20	54.1	20	1.73	4.47	45.93	1.3	1.66
30	32.2	30	1.51	5.48	67.83	1.48	1.83
40	21.7	40	1.34	6.32	78.33	1.6	1.89
50	13.1	50	1.12	7.07	86.93	1.7	1.94
60	0.3	60	-0.57	7.75	99.73	1.78	2

GRAPHICAL REPRESENTAITION OF KINEITCS OF DRUG RELEASE FROM OPTIMIZED TRIAL T-10

ZERO ORDER

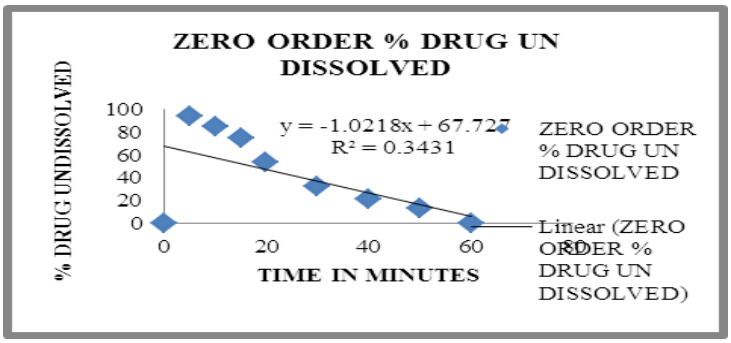

Figure no 12: Graphical representation of Zero Order Kinetics from trial T-10.

FIRST ORDER

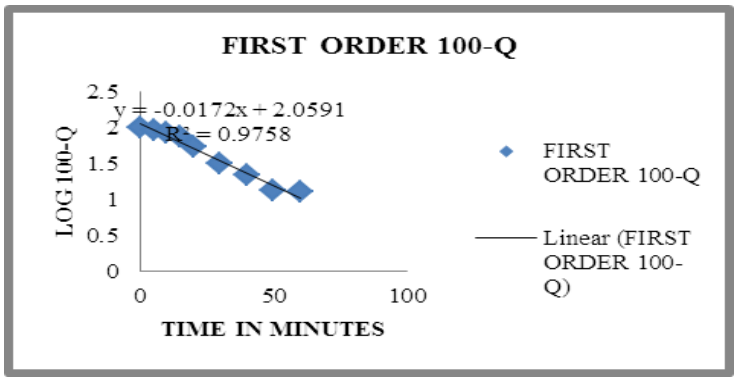

Figure no 13: Graphical representation of First Order Kinetics from trial T-10.

HIGUCHIS PLOT

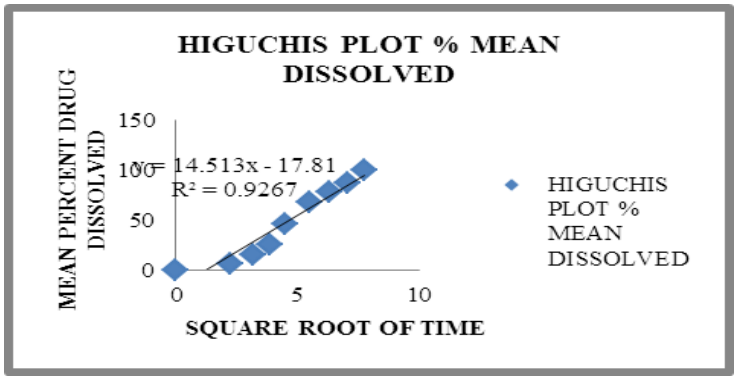

Figure no 14: Graphical representation of HIGUCHIS Order Kinetics from trial T-10.

KORESMEYER PEPPAS PLOT

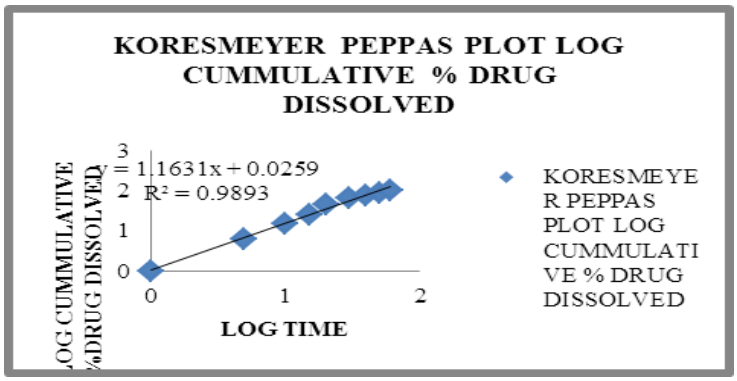

Figure no 15: Graphical representation of KORESMEYER-PEPPAS Order Kinetics from trial T-10.

DISCUSSION

In the present work API Zolmitriptan and other inactive ingredients were taken in to preparation based on the data of review of literature and FTIR spectra of API and other

inactive ingredients did not show much interference between the peaks of respective ingredients and API.

Based on the physicochemical properties of Zolmitriptan, melt granulation and direct compression techniques methods were applied in preparation of oral disintegrating tablets.

To attain an optimized formula in using melt granulation technique for the preparation of oral disintegrating tablets five trials were made of which trial T-5 was optimized where, all in-vitro parameters pertaining to oral disintegrating tablets was fulfilled. Similar situation is observed in case of direct compression technique and trial T-10 was optimized.

In case of melt granulation technique, there may be chances of losing the activity of the Zolmitriptan as, in the process, melting and reconstituting of its physical structure will take place.

Optimized trial T-10 was reproduced and taken for one month stability studies under controlled temperature and humilities.

Release rate of determined based on the R^2 values obtained after interpreting the drug release data with various kinetic models and the order of release of drug follows as KORESMEYER PEPPAS-0.989>FIRST ORDER-0.975>HIGUCHIS PLOT-0.926.

Based on the release rate kinetics data, the in-house prepared Zolmitriptan oral disintegrating tablets follows KORESEMEYER PEPPAS MODEL for release of the drug.

CONCLUSION

The in-house prepared oral disintegrating tablets showed promising results using different ingredients like precrol, ACE sulfate, Crosspovidone and Aerosil for all in-vitro evaluated parameters. Base on the results acquired formulation trial T-10 was optimized for further in-vivo studies.

ACKNOWLEDGEMENT

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"Formulation and In-Vitro Evaluation of Serotonin-5ht-1b and Serotonin-5ht-1d Receptor Agonist Agent-Zolmitriptan-An Anti-Migraine Drug"

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