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Solubility Enhancement and Formulation of Chronologically Triggered Pulsatile Press Coated Tablets of BCS II Drug - Zaltoprofen

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Abstract
Major drawback of several drug substances for oral delivery is poor solubility and gastrointestinal side effects. The present study was aimed at solubility enhancement and development of chronologically triggered pulsatile tablets of the poorly soluble drug zaltoprofen for the treatment of rheumatoid arthritis (RA) symptoms in the early morning.
Zaltoprofen (ZAF) solid dispersions (SDs) prepared by conventional solvent evaporation technique using novel Hydrophilic carriers PVPVA64, Soluplus and Lutrol surfactants and evaluated. The SDs prepared with PVPVA64 and Lutrol F127 in the ratio of 1:1.6:0.4 (ZAF: PVPVA64: Lutrol F127) increased the aqueous solubility of ZAF by 18.80-fold. 15 batches of Fast dissolving tablets (FDT) were prepared by direct compression method using super disintegrating agents. Out of 15 batches of FDTs ZC13 batch prepared with 8% of co processed super disintegrating agents produced rapid releases in 30 min (95%) with short disintegration time (47±1.91 Sec).Swellable top layer pulsatile press coated tablets prepared by using Konjac glucomannan (KGM) gum ,HPMC E50 and lactose and obtained 6hrs lag time before rapid release of drug in GIT.

Keywords
Zaltoprofen, pulsatile press coated tablets, PVPVA64, Soluplus, Solvent evaporation, Rheumatoid arthritis.

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INTRODUCTION:
Most of the existing and new drugs creates challenges for pharmaceutical industries in development of oral dosage forms due to its poor solubility, dissolution and which ultimately influences its bioavailability. According to Biopharmaceutics Classification System (BCS) low aqueous solubility and high permeability drugs classified as class II drugs (Kawabata et al., 2011). [1] Researchers have developed various systems several methods such as co-solvency, micronization, cyclodextrin inclusions, use of surfactants solid dispersions, use of salts, prodrug forms and use of polymorphs, micro emulsions and micro and Nano

disperse systems to encounter solubility problems which enhances dissolution and bioavailability of poorly soluble drugs. [2]

Improved dissolution and its speed of solid dispersions can be explained in general, one of the following mechanisms: eutectics formation, increase in drug's surface area by precipitation in the carrier, formation of a solid solution and better wettability due to the close contact with the hydrophilic carrier, precipitation as metastable crystalline form or decrease in the crystallinity of the substance. The properties of the drug and carrier, its combination and the method of preparation will decide the type of solid dispersion formed, Subsequently its solubility behaviour. [3]

Currently, PVP, PEG, PVPVA64, HPMC, HPMCC and Soluplus are the most widely used carrier in solid dispersion preparation because of its capability to form molecular adducts due to their strong hydrophilic properties with many drugs. The availability of hydroxyl and carbonyl group in monomeric units of these polymers tends to enhance the water solubility, drug's stability and bioavailability. It is accepted that presence of drug in glassy state in dispersion is the most desired state, since it improves its dissolution rate and drug absorption [4]. Several reports have been available on Soluplus and PVPVA64 as employed polymeric carriers to improve solubility of the poorly soluble drugs. For ex., Soluplus (polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer) increased the solubility of lornoxicam (75folds), Apripetant (5fold), Diacerin, Efavarinz, Giclazide etc while PVPVA64 (vinyl pyrrolidone–vinyl acetate copolymer) increased solubility of meloxicam, ketoprofen, tadalafil etc. [5-9]

Zaltoprofen (ZPF), is a 2-arylpropionic acids derivative, chemically it is 2-(10,11-dihydro-10-oxodibenzo (b, f) thiepin-2-yl) propionic acid (NSAIDs) having powerful activity against acute and chronic inflammation with less adverse effects in gastrointestinal tract than other NSAIDs [10]. Being unique drug, ZPF exerts anti-inflammatory and analgesic actions by cyclooxygenase-2 inhibition and bradykinin-induced 12-lipoxygenase inhibition, used for the treatment of rheumatoid arthritis and osteoarthritis, post-surgery or post trauma and tooth extraction and other inflammatory conditions [11-15]. According biopharmaceutics classification Zaltoprofen belongs to class II due to inheriting poor solubility and high permeability.

By comparison with conventional delivery systems, pulsatile systems under chrono-pharmaceuticals are very effective and received much attention globally with better patient compliance due to delivery of drug at specific place at the specified time in required amount after predetermined lag time. [16-19].

Pulsatile drug delivery system can be broadly classified into 4 classes.,

1. Time controlled pulsatile system
2. Stimuli induced pulsatile system
3. Externally regulated pulsatile system
4. Multi particulate systems. [20,21].

The present study is to enhance solubility by prepare solid dispersion by solvent evaporation method using novel hydrophilic carriers i.e. Soluplus, PVP VA68 and Lutrol surfactants preparation of Fast dissolving tablets (FDT's) to enhance dissolution rate, bioavailability and to prepare chronologically triggered pulsatile tablets for rapid release of drug after lag time (6 hrs).

MATERIALS AND METHODS:

Materials:

The materials used were as follows: Zaltoprofen (ZPF, gift sample from Ipca labs, India); PVP VA68, Soluplus, Lutrol F68, Lutrol 87, Lutrol F127 (gift samples from Hetero drugs, HYD), Microcrystalline Cellulose (MCC), spray dried Lactose, Croscarmellose Sodium, Crospovidone, Sodium starch glycolate (SSG), Hydroxy propyl methyl cellulose (HPMC E50), cellulose Acetate Propionate, Talc, Magnesium stearate, Konjac glucomannan (KGM). All chemicals were of HPLC or analytical grade.

EXPERIMENTAL METHODS:

Preparation of Standard curve:

50 milligrams of pure drug zaltoprofen (ZPF) was exactly weighed and it was dissolved with sufficient quantity of methanol in a 100 mL volumetric flask. and then volume adjusted to the mark with same to get standard stock solution (500 µg/mL of ZPF). From this, 1, 2, 3, 4, 5, 6 mL of transferred into sepearte100 mL volumetric flask, diluted with Phosphate buffer pH 6.8 or distilled water or 0.1N HCl up to the mark to obtain ZAF concentration ranging from 5-30 µg/mL and analysed for its absorbance at 243nm by using UV Double Beam Spectrophotometer [22,23]

Phase Solubility Studies:

According to Higuchi and Connors method of Phase-solubility studies, excess quantity of drug (25 mg) added to 25 ml of aqueous solutions of carriers (0.5%,1%, 1.5%, 2%, 2.5% and 3%).The suspensions was continuously shaken in mechanically, incubated another for 24hrs at 37 ± 2°C, separated, centrifuged it at 2000 rpm for 5 min and supernatant liquid separated, filtered and drug content was determined by UV-Visible double beam spectrophotometer at 243 nm. [24,26]

Solubility studies:

Solubility of ZAF and SDs in various media was carried out by equilibrium solubility method. Sufficient excess amount of ZAF was added separately to 5 mL of Distilled water, pH 1.2 0.1N HCl, PB pH 6.8 present in 10mL screw-capped glass vials. The vials were shaken on mechanical shaker (Lab India, Mumbai, India) at a temperature of 37 ± 2◦C, allowed it to equilibrate for 24 h, finally centrifuged for 5 min at 2000 rpm. The supernatant liquid was filtered and analysed for drug content by UV visible double beam spectrophotometer at 243nm [24-26].

Infrared Spectroscopy:

The incompatibility between drug and excipients was checked by FTIR spectra obtained on SHIMADZU 8400S, Japan. The finely milled pure drug (ZAF), mixed with potassium bromide, compressed to produce pellets and the resulted pellets scanned for Infrared radiation absorption over the wave number of 8000 to 400cm^{-1}. [27].

Formulation and evaluation of Zaltoprofen Solid Dispersion:

ZPF solid dispersion (SD) prepared by simple solvent evaporation method. According to composition (Table no:1),10 grams of ZAF and carrier alone or mixture (PVP VA64, Soluplus, Lutrol F68, Lutrol F87, Lutrol F127) weighed, powdered and finally dissolved in 25 ml methanol in a china dish with continuous stirring up to complete evaporation of solvent at 40˚c to obtain dry granules. The dry mass of SDs were dried in a vacuum oven at 40°C for 12 h, size reduced to granules [28].

Table No.1: Composition of Zaltoprofen solid dispersions

S.No	Formulation Code	Drug: Carrier (or) Carrier Mixture	Drug: Carrier Ratio
1	ZD	Zaltoprofen (ZAF)	--
2	ZSD1	ZAF: PVPVA 64	01:01
3	ZSD2	ZAF: PVPVA 64	01:02
4	ZSD3	ZAF: SOLUPLUS	01:01
5	ZSD4	ZAF: SOLUPLUS	01:02
6	ZSD5	ZAF: PVPVA 64: SOLUPLUS	01:01:01
7	ZSD6	ZAF: PVPVA 64: LUTROL F68	1:1.8:0.2
8	ZSD7	ZAF: PVPVA 64: LUTROL F87	1:1.8:0.2
9	ZSD8	ZAF: PVPVA 64: LUTROL F127	1:1.8:0.2
10	ZSD9	ZAF: PVPVA 64: LUTROL F68	1:1.6:0.4
11	ZSD10	ZAF: PVPVA 64: LUTROL F87	1:1.6:0.4
12	ZSD11	ZAF: PVPVA 64: LUTROL F127	1:1.6:0.4

Drug content and Yield:

Solid dispersion equivalent to 80 mg of ZAF was accurately weighed and dissolved in small quantity of methanol in volumetric flask (100 ml), volume was made up to mark with PB pH 6.8 and filtered. 1 ml of filtrate separated, diluted to 100 ml using PB pH 6.8 and analysed at 243 nm. Drug content was measured with help of standard curve, % Yield calculated using following equation.

$$\% \text{ Yield} = \frac{\text{Practical Yield}}{\text{Theotical Yield}} \times 100$$

Stability Constant and Gibb's Free Energy:

The stability constant (Ks) between each drug–carrier component in complex was calculated data from phase-solubility profile curve and using below equation:(31)

$$Ks = \frac{Slope}{So(1 - slope)}$$

The Gibbs free energy of transfer, ΔGo tr of drug in carrier and carrier mixture were calculated by utilising following relationship.

$$\Delta Go_{tr} = -2.303RT.log\ \frac{S_0}{S_s}$$

Where, So and Ss are solubilities of pure drug and SD in solvent respectively.

Surface morphology:

The shape and surface of the SDs was studied by using scanning electron microscopy (SEM), JEOL JSM 6390, England. The samples were fixed on mini aluminium stubs having double-sided tape, examined in the microscope at magnification of X500, X2000 with an accelerating voltage of 15 kV and working distance of 8 mm and.

Formulation and evaluation of fast Dissolving core Tablets:

ZAF FDT tablets were prepared by direct compression method. As per the formulation table (Table no:2,3) SD equal to 80mg of ZAF and excipients i.e. SDL, MCC,) Croscarmellose Sodium, Crospovidone, SSG, were pre-weighed accurately, separately sieved (60# sieve), mixed based on its weighed order, glidant, lubricant were added and finally compressed using Rimek compression Machine with 8mm sizes flat and round punches and analysed for quality control parameters like weight variation, Hardness, Friability, Disintegration time, wetting time [29,30].

Table no.2: Composition of ZAF fast dissolving core tablets (ZC1 –ZC8)

S.No	Ingredient	Composition of FDTs (mg)							
		ZC1	ZC2	ZC3	ZC4	ZC5	ZC6	ZC7	ZC8
1	S.D* (≈80mg of Zaltoprofen)	242	242	242	242	242	242	242	242
2	Crospovidone	7	14	21	28	--	--	--	--
3	sodium starch glycolate	--	--	--	--	7	14	21	28
4	Croscarmellose Sodium	--	--	--	--	--	--	--	--
5	Spray dried lactose	64	57	50	43	64	57	50	43
6	Micro crystalline Cellulose	30	30	30	30	30	30	30	30
7	Talc	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
8	Magnesium Stearate	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
Total weight of tablet (mg)		**350**	**350**	**350**	**350**	**350**	**350**	**350**	**350**

- % Weight variation calculated using the following formula

$$\%\ \text{weight variation} = \frac{\text{Avg weight} - \text{Individual weight}}{\text{Avg. Weight}} \times 100$$

- Hardness of tablets determined using Monsanto hardness tester
- Friability determined by using Roche friabilator and following formula

$$\%\ \text{Friability} = \frac{\text{Intitial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

- Disintegration time calculated using USP disintegration apparatus using 900mL of PB pH 6.8.
- Wetting time calculated by placing on filter paper present in small amount dye solution in petri dish.

***In-vitro* dissolution studies of solid dispersion and FDTs:**

The invitro dissolution studies of Pure drug ZAF (80 mg) and SDs (weight equivalent to 80 mg of ZAF) and FDTs were carried in USP dissolution apparatus II using 900 mL of PB pH 6.8 at 50 rpm 37°C, at regular time intervals 5ml of aliquots were withdrawn and filtered, checked for drug release by double beam spectrophotometrically at 243 nm. [32]

Study of Dissolution Parameters- (% DE), (MDT), $T_{50\%}$, $T_{75\%}$, $T_{95\%}$:

Some of the model independent parameters like dissolution efficiency (%DE), mean dissolution time (MDT), $T_{50\%}$, $T_{75\%}$, $T_{95\%}$ were calculated by using equations, using PCP Disso v3 software (Pune, India) and from dissolution graphs to check efficiency of optimised formulation with others. [33]

$$DE = \frac{\int_0^t y \times dt}{y100 \times t} \times 100\%$$

Where y = amount of drug release up to specific time 't'

$$MDT = \frac{\sum_{j=1}^{n} \hat{t}j\Delta Mj}{\sum_{j=1}^{n} \Delta Mj}$$

Where j = the sample number,
N = No of dissolution sample times,

t^j = Time at midpoint between tj and tj−1
ΔMj = Amount of drug released between 2 points

Formulation of Press coated pulsatile Tablets:

Pulsatile tablets were prepared by direct compression method using Rimek mini press with the composition as given in table no:4, by using 10mm flat tablet punch. Initially KGM gum, HPMC E50 and Lactose were weighed and mixed well, place in the bottom of die cavity and gently compressed. core tablet is placed at the centre on powder bed, cellulose acetate propionate added to cover sides and top of the core tablets and compressed to final pulsatile tablet. [34]

***Invitro* dissolution study of press coated tablets:**

The drug release studies of pulsatile tablets were conducted in pH 1.2 HCl (900 mL) media for 2 h , proceeded by PB pH 6.8 for about 3 hrs later, media was replaced with PB pH 6.8 containing 5% w/v rat cecal content for another 6 hrs using the USP dissolution apparatus at 37 ± 0.5°C and with paddle speed of 50 rpm. At regular intervals 5mL of aliquots were withdrawn and to maintain sink conditions, equal volume of fresh medium was replaced. The withdrawn samples were analysed for absorbance by spectrophotometrically at 243 nm [35,36]**.**

Pharmacokinetic study:

In a single-dose, open-label, cross over study used with 9 rabbits grouped randomly in 3 groups. White Rabbits weighing 1.4-1.6 kg were selected and supplied chow diet and water for about one week, their central ear vein was cannulated with proper anaesthesia using diethyl ether. The cannula was emptied properly and to prevent the blood clotting it was filled with heparinized isotonic saline (100 IU/mL). The rabbits were fasted at least 6 hr before the experiment, with free access to water. Optimised press coated tablet and marked FDT tablet (Equal to 8 mg of zaltoprofen) was administered orally with 5 mL of distilled water. At specific time intervals 1 mL of blood was collected for cannula, 0.2 mL of heparinized 0.9% NaCl solution was added, mixed properly and centrifuged at 2500 rpm for about 40mi.The plasma was collected and analysed by HPLC. The pharmacokinetic parameters ($AUC_{0\text{-}22h}$, $AUC_{0\text{-}\infty}$, K_E, Vd, $T_{1/2}$, C_{max}, T_{max}, CL) computed by non-compartmental analysis using PK Solver software. [37,38]. The above study approved by IAEC of PRRM college of pharmacy, Kadapa, Andhra Pradesh, with the file no:1423/PO/a/11/CPCSEA/316/2014.

RESULTS AND DISCUSSION:

Standard curve:

The UV absorbance of ZAF was determined at of 243 nm in different media were plotted graph against its concentrations **(**Fig.1**).** It was observed that ZAF showed increment in absorbance with concentration, showed linearity. The regression values (R^2) for ZAF in distilled H_2O, HCl, PB pH 6.8, PB pH 7.4 were found to be 0.9987, 0.9989, 0.9994, 0.9991 respectively. Hence ZAF obeyed Beer-Lambert's law (5-30 µg/mL) and useful for further drug content determinations.

Results of Phase Solubility studies:

According to higuchi and Connors method, the phase solubility studies of ZAF with different carriers PVPVA 64, Soluplus and Carriers with surfactants Lutrol F68, Lutrol F87, Lutrol F127 in distilled H_2O were carried out and it was found that ZAF solubility increased linearly with respect to carrier concentration fig.no:2. The phase diagram was shown typical A_L type graph with first order chrematistics as per Higuchi and Connors. The apparent stability constant of for all SDs was in the range from 1.41 to 2.8 indicated good stability of complex. The ZSD11 prepared with ZAF, PVPVA64, Lutrol F127 (1:1.6:0.4) maintained highest value.

Infrared spectroscopy:

The FTIR graph of pure ZAF compared with reference for specific functional groups and confirmed its identity. It was observed absorption peaks in pure drug and formulation, no much difference observed therefor it could be concluded that there was no strong interaction between drug and excipients.

Results of solubility Studies:

The solubility of pure drug ZAF has been studied in different solvents like distilled H_2O, 0.1N HCl, PB pH 6.8 it has been found 0.15 mg/mL, 0.013 mg/mL, 0.851 mg/mL respectively. The solid dispersions ZSD1 & ZSD2 prepared by using PVPVA64 shown higher solubilities (7.07-fold,11.61-fold) than SDS prepared with Soluplus (ZSD3, ZSD4 – 5.82-fol,8.27-fold res.,) in distilled water. Lutrol surfactants showed good improvement in ZAF solubility along with PVPVA64. For ex. ZSD11 prepared with and PVPVA64 & Lutrol F127 increased the ZAF solubility by 18.80-fold,19.31-fold, 18.77-fold respectively in H_2O, 0.1N HCl, PB pH 6.8. Table no:5**.**

Gibb's Free Energy and Drug content:

The Gibbs free energy (ΔG tr) values calculated using solubility data were given in table no:6. All the SDs showed negative values which were increases from -

4951.88 to -7473.36 kJ/mol. It understood that all SDs spontaneously solubilizing ZAF in media. The drug content of all dispersion ZSD1-ZSD11 was found in between 96.19 % to 99.64% and specifies complete mixing of drug within carrier complex and minimum loss of pure drug. From the Solubility and Gibbs free energy data it evidenced that ZAF solubility has been increased with carrier and surfactants concentrations.

Surface morphology:

SEM photographs of optimised dispersion ZSD11 were given in fig no:3**.** The surface of particle was uniformity with small dispersed pits reveals complete mixing of drug and excipients, pits were formed due to it evaporation of solvent droplets.

Results of solid dispersion dissolution studies:

The invitro dissolution studies of pure ZAF and SDs conducted, data presented in table no:7 & 8. whereas dispersions (ZSD1 & ZSD2) prepared with PVPVA64 showed much higher drug release compared to SDs prepared with Soluplus (ZSD3 & ZSD4). It has been proved that solubility and dissolution of ZAF significantly enhanced by PVPVA64 than Soluplus. Further it also observed that PVPVA64 & Lutrol surfactants combinations employed to prepare SDs from ZSD6-ZSD11, significantly improved its release. Out of 11 SDs prepared, LSD11 showed rapid drug release i.e. 45% in 5 min and 99.91 % in 45min.

Dissolution Parameters- (% DE), (MDT), $T_{50\%}$, $T_{75\%}$, $T_{95\%}$:

Non compartmental, Model independent parameters useful for comparison of formulations effectiveness were computed using equations and by PCP Disso. v3 software (Pune, India), results were tabulated in table no:6**.** By comparing all SDs, it was notice that LSD11 showed highest values i.e., 40.42, 63.88 for $\%DE_{10}$ and $\%DE_{20}$ whereas lowest MDT, $T_{50\%}$, $T_{75\%}$, $T_{95\%}$ value i.e. 7.61min,5.92 min, 10.94, 19.38min. based on this non compartmental parameters, surfactant Lutrol F127 is very effective in improved the drug release.

Evaluation of fast Dissolving Tablets:

The prepared 15 batches (ZC1-ZC15) of FDTs by direct compression were analysed for *invitro* quality by several Q.C tests i.e., weight variation, hardness, friability, disintegration time, wetting time and results were successfully placed in Table no:9. Based on the data ,the Average weight of FDTs ranges was from 348.68±2.89 mg-351.33±2.15mg , % friability ranges from 0.25 to 0.957%, Hardness ranges from 3.83 to 4.33 kg/cm^2 which indicates uniformity in tablets weight with good resistance to break .Most importantly FDTs displayed variable wetting time, disintegration times as in the range of 41-281 seconds and in the range of 47 to 297 seconds respectively. By comparing the all the parameters ZC13 batch prepared by using mixture of disintegrating agents i.e. 6%w/w Crosspovidone,1%w/w Crosmellose Sodium,1% w/w SSG, it was found to better FDT which was disintegrated rapidly in 47sec.

Results of FDTs Dissolution studies:

Dissolution studies of 15 batches of FDTs conducted in USP disso apparatus II using PB pH 6.8 and obtained results were given in fig no:5&6. The data represents the FDTs drug release indicates that all 15 batches release the as less as 90% in 60 min with significant variation in drug release initially. Compared to other FDTs, ZC13 formulation prepared with mixture of disintegrants which disintegrated firstly has shown faster drug release i.e. 68.23% in 10 min and 99.33% in just 30 min.

Results of pulsatile tablets evaluation:

In order to release the drug with predetermined time lag, FDT tablets were converted to pulsatile tablets.3 sides of FDT core tablets were coated in soluble and impermeable cellulose acetate propionate and one side i.e. top side coated with mixture of KGM, lactose and HPME E50 by press coating technology. 4 batches of pulsatile tablets were formulated and tested for post compression parameters like Average weight, Thickness, Hardness, Friability, Swelling and *invitro* release study, table no:10. The average weight of pulsatile tablets was very close to 600mg with highest standard deviation of 4.386 and has <1 % friability, 5.15- 5.37mm thickness, 5.92-6.17 kg/cm^2 hardness. pulsatile tablets from ZP1 to ZP4 showed much variation in Swelling index values i.e. 36.31% to 28.26 % from ZP1 to Zp4 respectively which reveals that as the concentration of KGM gum decreases, the swelling index of pulsatile tablet decreased. Form the results of dissolution studies fig no:7. all the pulsatile tablets were rapidly releasing nearly 70% of drug with varied lag time (6 – 9.5 hrs). The lag time before pulsatile release was directly depended and proportional to KGM gum concentration in swellable top layer. Hence by varying the KGM gum concentration in swelling layer we can modulate the lag time which was very essential to treat the patients effectively in the early morning with bedtime doing of tablets.

Pharmacokinetic studies:

The plasma drug concentration of ZPF from marketed IR tablet and optimised pulsatile tablet (ZP4) with respective to time was calculated and shown in Fig no:8**.** The pharmacokinetic parameters ($AUC_{0\text{-}22h}$, $AUC_{0\text{-}\infty}$, K_E, Vd, $T_{1/2}$, C_{max}, T_{max}, CL) of ZP4 and

marketed IR tablet were determined by non-compartmental analysis using PK Solver software. Table no:11.The obtained C_{max}, T_{max} & $AUC_{0-\infty}$ values for optimised tablet were 17.44 ± 1.223 µg/mL, 8 hr and 99.3 ± 12.327 µg h/mL respectively and the same values for the marketed tablet were found to be 15.02 µg/mL, 1.5 h and 81.12 ± 6.854 µg h/ mL respectively. The MRT of optimised and marketed IR tablets was found to be 10.62 ± 0.434 hr, 5.2842 hr. Pharmacokinetic parameters shown a statistically significant difference in the value of MRT, Cmax, T_{max} including lag time between optimised ZAP4 tablets and marketed IT tablets.

Table no.3: Composition of ZAF fast dissolving core tablet (ZC9-ZC15)

S.No	Ingredient	Composition of FDTs (mg)						
		ZC9	ZC10	ZC11	ZC12	ZC13	ZC14	ZC15
1	S.D* (≈80mg of Zaltoprofen)	242	242	242	242	242	242	242
2	Crospovidone	--	--	--	--	21	14	7
3	sodium starch glycolate	--	--	--	--	3.5	7	10.5
4	Croscarmellose Sodium	7	14	21	28	3.5	7	10.5
5	Spray dried lactose	64	57	50	43	43	43	43
6	Micro crystalline Cellulose	30	30	30	30	30	30	30
7	Talc	3.5	3.5	3.5	3.5	3.5	3.5	3.5
8	Magnesium Stearate	3.5	3.5	3.5	3.5	3.5	3.5	3.5
Total weight of tablet (mg)		**350**	**350**	**350**	**350**	**350**	**350**	**350**

Table no.4: Composition of press coated pulsatile tablet.

S.No	Ingredients	ZP1	ZP2	ZP3	ZP4
1	Core Tablet (Z-FDT*)	350	350	350	350
2	KGM Gum	80	70	60	50
3	Lactose	10	20	30	40
4	HPMC E50	10	10	10	10
5	Cellulose Acetate Propionate	146	146	146	146
6	Talc	2	2	2	2
7	Megnesium Stearate	2	2	2	2
Total Weight of Tablet (mg)		**600**	**600**	**600**	**600**

Table no.5: solubility data of ZAF and solid dispersions in different media.

S.D. CODE	SOLUBILITY (mg/mL) (Mean±SD, n=3)					
	Distill water (mg/mL) (Mean±SD)	No of fold Solubility Increased 'n'	0.1N Hcl (mg/mL) (Mean±SD)	No of fold Solubility Increased 'n'	Phosphate Buffer 6.8 (mg/mL) (Mean±SD)	No of fold Solubility Increased 'n'
ZD	0.015±0.001	--	0.013±0.001	--	0.851±0.006	--
ZSD1	0.106±0.003	7.07	0.088±0.001	6.79	7.105±0.008	8.35
ZSD2	0.174±0.004	11.61	0.145±0.002	11.16	11.693±0.042	13.74
ZSD3	0.087±0.001	5.82	0.073±0.001	5.63	5.426±0.034	6.38
ZSD4	0.124±0.002	8.27	0.104±0.001	7.97	8.373±0.023	9.84
ZSD5	0.123±0.008	8.18	0.092±0.001	7.04	6.399±0.024	7.52
ZSD6	0.218±0.002	14.53	0.178±0.002	13.71	13.846±0.017	16.27
ZSD7	0.226±0.003	15.05	0.186±0.001	14.28	13.628±0.026	16.01
ZSD8	0.259±0.002	17.28	0.209±0.001	16.08	15.828±0.02	18.60
ZSD9	0.236±0.004	15.76	0.201±0.002	15.46	14.57±0.133	17.12
ZSD10	0.249±0.004	16.62	0.215±0.004	16.51	14.718±0.169	17.30
ZD11	0.282±0.003	18.80	0.251±0.002	19.31	15.975±0.009	18.77

Table No.6: Evaluation parameters of ZAF solid dispersions.

S.D Code	Gibbs Free Energy ΔG tr (kJ/mol)	Drug content (% w/w) (Mean ± SD)	% Yield (Mean ± SD)	$T_{50\%}$	$T_{75\%}$	$T_{95\%}$	$\%DE_{10}$	$\%DE_{20}$	MDT
ZD	--	--	--	76.76	151.25	210.83	8.86	15.95	18.44
ZSD1	-4951.88	98.58±0.39	94.78±0.51	13.92	25.79	83.61	19.65	35.26	13.99
ZSD2	-6230.56	98.67±0.44	95.91±0.54	8.31	24.32	75.79	29.05	43.36	12.42
ZSD3	-4449.96	96.19±1.41	96.29±0.39	19.31	51.38	104.24	16.94	29.15	16.98
ZSD4	-5355.8	98.83±0.83	95.37±0.47	18.72	43.46	91.87	21.01	33.76	16.38
ZSD5	-5328.17	96.51±0.89	93.85±0.32	11.62	32.17	141.13	24.37	37.91	13.4
ZSD6	-6808.37	99.17±0.42	96.15±0.54	10.64	20.84	44.40	24.95	44.17	12.99
ZSD7	-6900.15	98.32±0.4	96.77±0.5	11.38	19.15	30.07	25.02	43.43	12.11
ZSD8	-7255.47	99.64±0.26	95.83±0.11	7.10	13.61	27.63	35.95	56.21	9.73
ZSD9	-7017.99	96.87±1.75	98.14±0.59	10.16	18.90	37.88	27.41	47.01	12.73
ZSD10	-7156.03	93.63±0.7	97.83±0.56	9.41	16.72	29.47	27.51	48.39	11.96
ZSD11	-7473.36	99.18±0.61	97.13±0.44	5.92	10.94	19.38	40.42	63.88	7.61

Table no.7: Dissolution data of solid dispersions batches ZD-ZSD5

Time (Min)	% Cumulative Drug Release (Mean ± SD, n=6)					
	ZD	ZSD1	ZSD2	ZSD3	ZSD4	ZSD5
0	0±0	0±0	0±0	0±0	0±0	0±0
5	8.84±0.26	19.57±2.35	32.04±2.61	19.54±2.01	24.02±0.98	28.24±1.39
10	17.75±1.56	39.44±2.11	52.11±1.55	28.67±2.53	35.99±0.54	40.99±2.40
15	23.94±2.10	52.9±1.14	58.37±1.49	42.48±0.64	48.27±1.04	53.31±1.13
20	26.57±0.47	58.28±0.48	61.83±2.07	51.85±0.95	53.53±0.99	58.22±0.78
25	31.68±1.40	73.94±1.39	77.08±2.22	65.32±1.53	67.32±0.38	65.27±2.12
30	33.96±0.26	80.63±2.20	83.15±2.25	67.81±1.03	71.60±1.03	74.69±0.41
45	40.35±0.60	82.25±0.37	85.42±0.75	72.17±1.49	75.74±0.26	77.20±0.27
60	43.71±0.52	84.68±1.11	87.83±0.47	78.82±0.40	82.98±0.69	80.18±1.05

Table no.8: Dissolution data of solid dispersions batches ZSD6-ZSD11

Time (Min)	% Cumulative Drug Release (Mean ±S D, n=6)					
	ZSD6	ZSD7	ZSD8	ZSD9	ZSD10	ZSD11
0	0±0	0±0	0±0	0±0	0±0	0±0
5	26.11±2.02	27.46±0.66	40.03±2.4	30.16±1.62	28.82±1.24	45.25±2.01
10	47.58±0.68	45.17±1.07	63.72±1.01	49.33±2.11	52.37±1.6	71.20±1.63
15	66.48±0.92	62.66±0.89	79.34±1.72	70.41±1.18	72.51±2.04	91.31±1.86
20	73.04±2.06	76.83±1.57	83.47±1.28	76.29±1.47	79.74±1.62	95.52±0.91
25	84.79±1.49	87.62±1.12	92.20±0.39	87.63±1.26	90.82±1.80	96.27±0.61
30	92.73±0.64	94.99±0.31	97.53±0.76	93.27±1.17	95.49±0.84	98.89±0.24
45	95.22±0.77	97.02±0.69	98.70±0.51	96.56±1.02	97.31±1.40	99.91±0.05
60	97.33±0.49	96.64±1.13	99.35±0.19	99.32±0.27	99.55±0.39	

Table no.9: Post compression test results of ZAF fast dissolving tablets.

Batch	Avg.weight (Mean±SD) (mg)(n=20)	Thickness (Mean±SD) (mm)(n=6)	Hardness (Mean±SD) (Kg/cm^2)(n=6)	Friability (Mean±SD) (%)(n=3)	Disint.Time (Mean±SD) (Sec)(n=6)	Wet.Time (Mean±SD) (Sec)(n=6)
ZC1	350.66±1.52	3.37±0.109	3.83±0.236	0.582±0.131	253±9.911	238±3.35
ZC2	349.74±2.17	3.51±0.1	4.08±0.186	0.379±0.122	165±5.439	150±8.596
ZC3	349.80±1.59	3.42±0.102	4±0.289	0.637±0.187	101±2.775	92±7.819
ZC4	350.97±1.77	3.4±0.065	4.33±0.373	0.498±0.129	70±3.217	59±6.823
ZC5	351.33±2.15	3.52±0.114	3.92±0.186	0.359±0.102	297±4.989	281±9.978
ZC6	349.85±1.74	3.48±0.049	4.17±0.236	0.957±0.128	225±4.3	212±6.568

ZC7	348.93±2.24	3.49±0.057	4.17±0.373	0.393±0.145	137±3.6	121±4.81
ZC8	350.38±1.22	3.46±0.102	3.92±0.186	0.602±0.319	95±3.811	80±2.887
ZC9	349.81±2.29	3.55±0.136	3.83±0.236	0.519±0.078	302±6	274±8.282
ZC10	350.98±1.91	3.42±0.099	4.08±0.186	0.25±0.112	179±3.883	162±5.871
ZC11	350.85±2.46	3.48±0.065	4.1±0.224	0.485±0.226	103±2.489	96±3.055
ZC12	348.68±2.89	3.44±0.065	4.08±0.186	0.617±0.132	79±3.685	63±4.298
ZC13	349.96±1.90	3.46±0.118	3.92±0.186	0.51±0.206	47±1.915	41±3.416
ZC14	349.60±2.76	3.47±0.118	3.83±0.236	0.837±0.098	72±2.011	64±4.384
ZC15	350.71±1.68	3.45±0.1	4.08±0.186	0.277±0.04	86±2.241	71±3.819

Table no.10: Post compression properties of pulsatile tablets

Code	Avg.weight (mg) (Mean±SD)n=20	Thickness (mm) (Mean±SD)n=3	Hardness (kg/cm^2) (Mean±SD)n=6	Friability (%) (Mean±SD)n=3	Swelling Index (%) (Mean±SD)n=6
ZP1	599.78±2.474	5.15±0.025	6.17±0.236	0.073±0.006	36.31±2.58
ZP2	600.87±1.728	5.37±0.034	6.08±0.186	0.082±0.014	32.86±1.04
ZP3	597.99±4.386	5.35±0.159	5.92±0.186	0.104±0.026	29.4±1.26
ZP4	598.91±3.678	5.29±0.058	6±0.289	0.124±0.044	28.26±1.41

Table no.11: Pharmacokinetic parameters of zaltoprofen marketed IR tablet and optimised pulsatile formulation.

Parameter	Marketed IR Tablet (Mean±SD) n=3	Optimised Tablet (Mean±SD) n=3
KE (1/h)	0.2329 ± 0.022	0.2052 ± 0.024
$t_{1/2}$ (Hrs)	3.0053 ± 0.308	3.4216 ± 0.377
T_{max} (Hrs)	1.5 ± 0	8 ± 0
C_{max} (µg/ml)	15.02 ± 1.308	17.44 ± 1.223
AUC $_{0-t}$ (µg/ml*h)	80.51 ± 6.737	95.91 ± 11.138
AUC $_{0-\infty}$ (µg/ml*h)	81.12 ± 6.854	99.3 ± 12.327
MRT (Hrs)	5.2842 ± 0.186	10.62 ± 0.434
Vd (µg/ml)	0.4284 ± 0.034	0.4001 ± 0.04
CL ((µg/ml)/h)	0.0994 ± 0.009	0.0818 ± 0.01

Fig.no 1: Zaltoprofen standard in phosphate buffer pH 6.8.

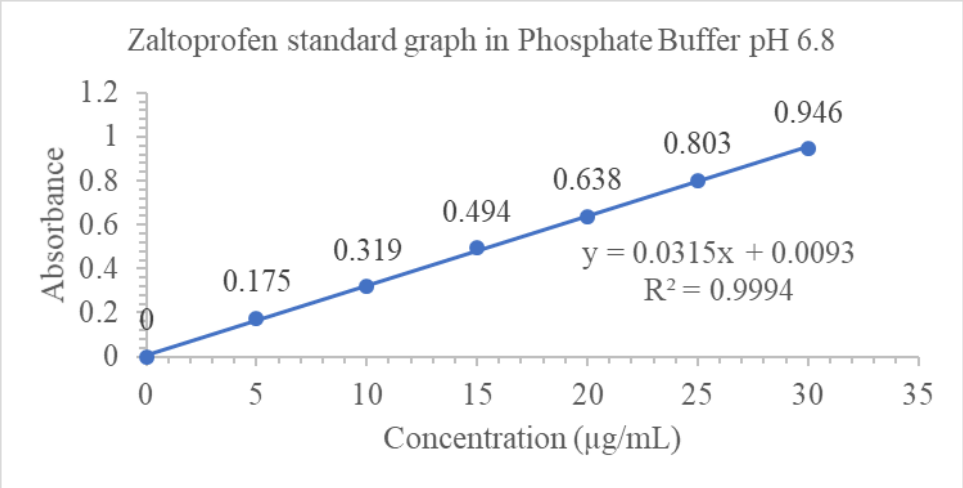


Fig no.2: Comparative dissolution profiles of zaltoprofen solid dispersions.

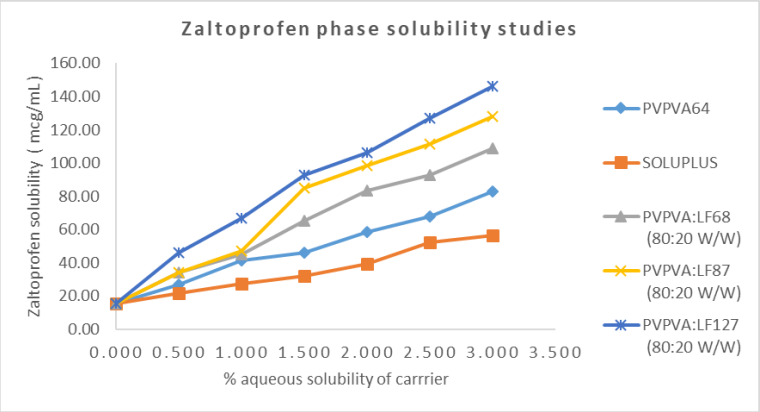


Fig no.3: comparative dissolution profiles of zaltoprofen solid dispersions.

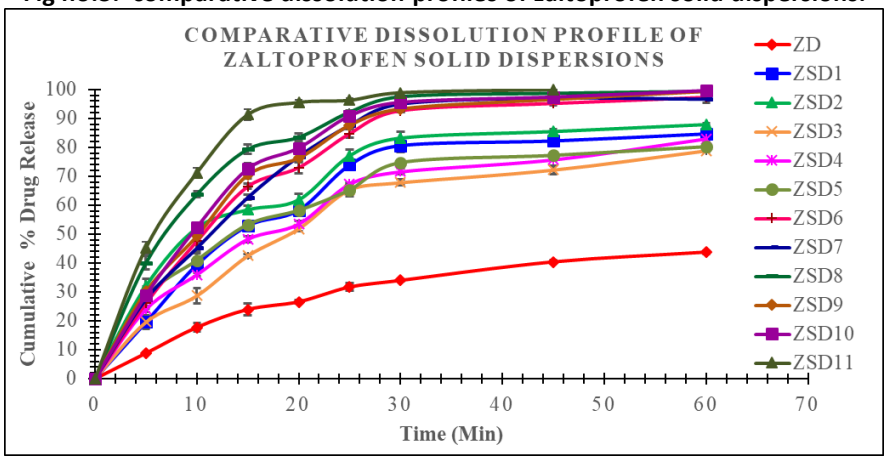


Fig no.4: SEM photographs of ZSD11 solid dispersion.

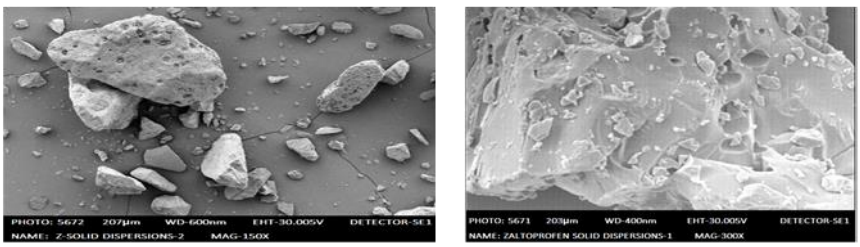


Fig no. 5: Dissolution profile of zaltoprofen FDTs (ZC1-ZC8)

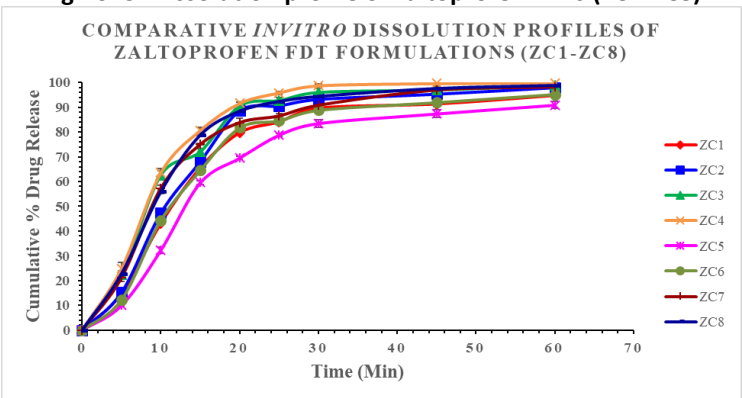


Fig no.6: Dissolution profile of zaltoprofen FDTs (ZC9-ZC15)

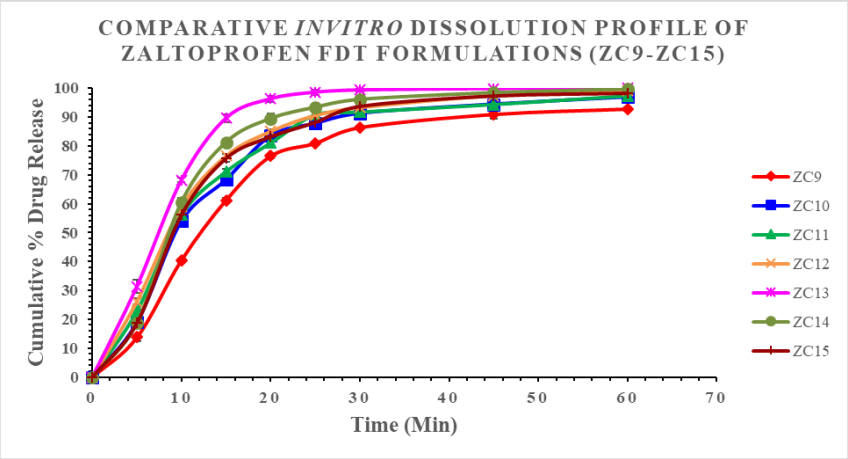


Fig no.7: Results of dissolution studies of Zaltoprofen pulsatile tablets

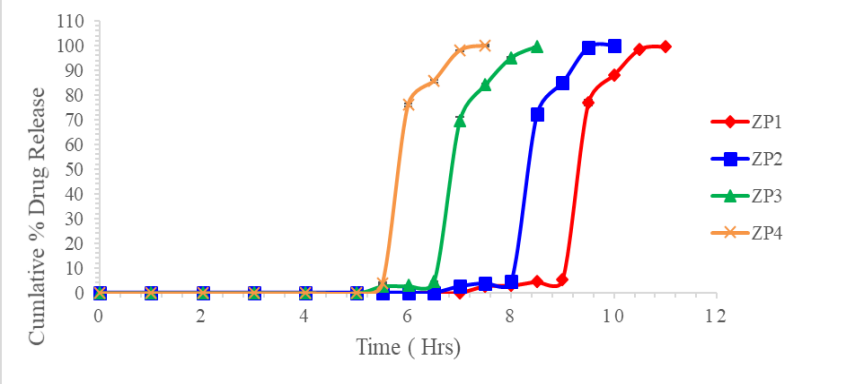
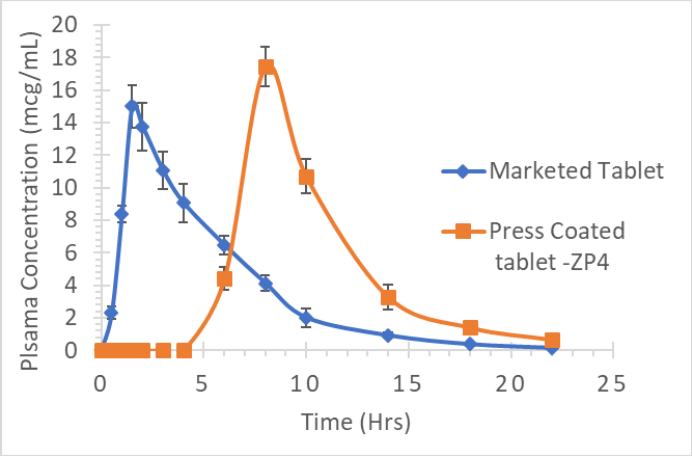


Fig no.8: Comparison of mean plasma concentration profile of zaltoprofen marketed Immediate release tablet with Optimised tablet.



CONCLUSION:

Several drug which are effectively used in treatment of many diseases and drugs which are under present investigation facing bioavailability problems due to its poor solubility and dissolution. Zaltoprofen is chemically an aryl propanoic acid derivative categorised under BCS-II class due to its poor solubility and high permeability. In order to enhance its solubility, 11 batches of solid dispersion were prepared using PVPVA64, Soluplus and Lutrol

surfactants. The SDs ZSD11 prepared with PVPVA64 and Lutrol 127 in the ratio of 1:1.6: 0.4 enhanced ZAF solubility by 18-fold. Further the dissolution could be improved by preparation of FDT tablets using super disintegrants. Out of 15 FDT tablets ZC13 tablets showed lesser disintegration time (47sec) and released the 99.9% of drug in just 45 min. The optimised FDT tablets ZC13 were further converted to press coated pulsatile tablets for release of drug with predetermined lag time. Out of 4 pulsatile press coated tablets ZP4 tablets has been showed 6hr lag time. The optimised press coated tablets was checked for *in vivo* effectiveness when compared with marketed IR tablet and found statistically significant higher values for optimised tablets than marketed IR tablet.

CONFLICT OF INTEREST: The authors declare no conflicts of interest.

REFERENCES:

[1]. Jin-Seok Choi, Jeong-Sook Park., Design of PVP/VA S-630 based tadalafil solid dispersionto enhance the dissolution rate.1-38. doi: 10.1016/j.ejps.2016.11.030
[2]. K.Ravi Shankar, K.P.R. Chowdary., Formulation development of efavirenz tablets employing β-Cyclodextrin, soluplus and pvp k30: factorial study. Int. Res J Pharm. App Sci,3(4):110-115, (2013)
[3]. Sue May Lim1, Zyu Wenn Pang., Enhancement of docetaxel solubility using binary and ternary solid dispersion systems. Drug Dev Ind Pharm, Early Online: 1–9.
[4]. Kamble Sharad K and Shinde Sunita S., Design and Development of Fast Dissolving Tablet of Gliclazide. Develop Drugs, 6(3): 000177, (2017)
[5]. Maha marzouk,Amal ammar,et al., preformulation development and invitro study of bilayer tablets of lornoxicam. Asian j pharm hea sci.oct-dec,7(4):1769, (2017)
[6]. Jinwen Liu, Meijuan Zou, Hongyu Piao. Characterization and Pharmacokinetic Study of Aprepitant solid dispersions with Soluplus. Molecules, 20:11345-11356, (2015)
[7]. Gaurav Pandit Sonaje1, KL Senthil Kumar., Development and Characterization of Diacerein Solid Dispersion through Spray Drying using a novel amphiphillic polymer Soluplus. Journal of Current Pharma Research, 6 (1):1699-1711(2015)
[8]. Siok-Yee Chan, Yin-Ying Chung., The characterization and dissolution performances of spray dried solid dispersion of ketoprofen in hydrophilic carriers. asian journal of pharmaceutical science,10:372–385, (2015)
[9]. Abbe Hasera, Tu Caoa., In situ Salt Formation During Melt Extrusion for Improved Chemical Stability and Dissolution Performance of a Meloxicam-Copovidone Amorphous Solid Dispersion. Molecular Pharmaceutics.2-47.
[10].Bussemer, T. Dashevsky, A., Journal of Controlled Release, 93:331–339, (2003)
[11].Hirate K, Uchida A, Ogawa Y, Arai T, Yoda K., Zaltoprofen, a nonsteroidal anti-inflammatory drug, inhibits bradykinin-induced pain responses without blocking bradykinin receptors. Neurosci Res,54: 288-94, (2006)
[12].Shigeru F, Nobuyoshi A, Emiko K.,Involvement of CYP2C9 and UGT2B7 in the metabolism of zaltoprofen, a nonsteroidal anti-inflammatory drug, and its lack of clinically significant CYP inhibition potential. J Clin Pharmacol,54: 295-303, (2002)
[13].Japanese Pharmacopoeia XV. Society of Japanese Pharmac. 15 Ed:242-4, (2006)
[14]. Kameyama T, Nabeshima T, Yamada S, Sato M., Analgesic and anti-inflammatory effects of 2-(10,11-dihydro-10-oxo-dibenzo [b,f] thiepin-2-yl)propionic acid in rat and mouse. Drug Res,37:19-26, (1987)
[15].Muratani T, Doi Y, Nishimura W., Preemptive analgesia by zaltoprofen that inhibits bradykinin action and cyclooxygenase in a post-operative pain model. Neurosci Res,51:427-3, (2005)
[16].Arvidson NG, Gudbjornson B., Circadian rhythm of secum interleucin-6 in rhematiod arthritis. Ann Rheum Dis,53:521–524, (1994)
[17].Barnes JP.Circadian variation in airway function. Am J Med 9:5–9,(1985)
[18].Fox KM, Mulcahy DA., Circadian rhythms in cardiovascular diseases. Postgrad Med J,67: S33–S36, (1991)
[19]. Millar-Craig MW, Bishop CN, Raftery EB., Circadian variation of blood pressure. Lancet,1:795–797,(1978)
[20].Gupta Nitan Bharti. Sharma Pooja., pulsatile drug delivery as modified release dosage form. a review. Journal of Drug Delivery & Therapeutics, 2(6):102-110, (2012)
[21].Chourasia, M.K. and Jain, S.K. J. Pharm. Pharm. Sciences,6:33, (2003)
[22].Kiran B. Aher, Girija B. Bhavar., Economical spectrophotometric method for estimation of zaltoprofen in pharmaceutical formulations. Pharm Methods, 2(2): 152–156, (2011)
[23].Sridhar Rao. K, Sreekanth. J. Zaltoprofen fast disintegrating tablets: formulation and in-vitro evaluation studies. International Journal of Pharmacy and Biological Sciences,6(2):122-129, (2016)
[24].Higuchi, T. and Connors, K.A., Phase-solubility techniques.Adv. Anal. Chem. Instrum, 4: 117- 212, (1965)
[25].F. Veiga a, J.J.C. Teixeira-Dias b., Inclusion complexation of tolbutamide with fl-cyclodextrin and hydroxypropyl-fl-cyclodextrin: International Journal of Pharmaceutics. 126: 63-71. (1996)
[26].Shailendra Singh Solanki., Study on mixed solvency concept in formulation development of aqueous injection of poorly water-soluble drug. Journal of pharmaceutics,1:1-8. (2013)

[27].Atul P. Sherje, Forum Patel., Study on effect of L-arginine on solubility and dissolution of Zaltoprofen: Preparation and characterization of binary and ternary cyclodextrin inclusion complexes. https://doi.org/10.1016/j.cplett.2018.01.025.
[28].M.najmuddin, Tousif khan., Enhancement of dissolution rate of ketoconazole by solid dispersion technique. International journal of pharmacy and pharmaceutical sciences. 2(3):132-136,(2010)
[29].N. G. Raghavendra Rao.,Development of fast dissolving nimodipine tablets: effect of functionality of super disintegrants. Journal of Pharmacy Research,4(9):2957-2962,(2011)
[30].Rajesh S. Jadon, Swadesh Nayak., Taste masking of Lornoxicam by polymer carrier system and formulation of oral disintegrating tablets: International Journal of Drug Delivery,1:27-31,(2009)
[31].Shirse Prabhakar.,formulation and evaluation of fast dissolving tablets of cyclodextrin inclusion complexed water insoluble drug:glimiperide.IJRAP.3(3), (2012)
[32].M.najmuddin., Tousif khan. Enhancement of dissolution rate of ketoconazole by solid dispersion technique. International journal of pharmacy and pharmaceutical sciences. 2(3):132-136, (2010)
[33].Paulo coasta., modelling and comparison of dissolution profiles.European jouranal of pharmaceutical sciences,13:213-233,(2001)
[34].Prashant A. Borgaonkar., Formulation and Evaluation of Pulsatile Drug Delivery System of Metoprolol Tartarate Using Core in Cup Tablet. American Journal of Medicine and Medical Sciences, 2(6): 114-122, (2012)
[35].BK Garg1, G. Gnanarajan., Formulation and Evaluation of pulsatile drug delivery system of rosuvastatin calcium using different swelling polymers. The pharma innovation,1(7):61-67, (2012)
[36].Om Prakash Ranjan et al., Optimization of Chronomodulated Delivery System Coated with a Blend of Ethyl Cellulose and Eudragit L100 by Central Composite Design: In Vitro and In Vivo Evaluation. Pharm Innov,9:95–105, (2014)
[37].Hari Krishna E, Rama Mohan Gupta V., Pharmacokinetic study of zaltoprofen spherical agglomerated dense compacts canvassed with commercial product. Clinic Pharmacol Biopharm,2(1):1000107, (2013)
[38].Hyun Kyoung Yang,a Seo Young Kim., Application of column-switching HPLC method in evaluating pharmacokinetic parameters of zaltoprofen and its salt. Biomed. Chromatogr,23: 537–542, (2009)