"ENHANCING INVITRO DRUG RELEASE OF PIOGLITAZONE USING SUPERDISINTEGRANTS-FDT"

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Abstract

The objective of the present study was to prepare fast dissolving tablets of a hypoglycemic drug Pioglitazone hydrochloride using solid dispersion. One of the major problems with this drug is its low solubility, which results in poor bioavailability after oral administration. The solubility of poorly soluble drug was enhanced by preparing solid dispersions of the drug by PEG 4000 as carrier. Solid dispersion formulations were prepared using different ratios of drug and carrier i.e. 1:1, 1:2: 1:3 and 1:4; respectively by conventional solvent evaporation method. The optimized solid dispersions were further kneaded with suitable proportions of superdisintegrants such as Crosspovidone, Sodium starch Glycolate, Crosscarmellose sodium and different diluents avicel, mannitol and lactose etc. FT-IR spectroscopy, differential scanning calorimetry and U.V spectroscopy, solubility determination, partition coefficient etc studies were carried out in order to characterize the drug and solid dispersion and it showed no evidence of drug-excipient interaction. The prepared formulations were evaluated for thickness, hardness, friability, weight variation, water absorption ratio, wetting time, in-vitro disintegration time and in-vitro dissolution studies. The maximum drug release was found in formulation PGHT8 (97.842%). It was concluded that fast dissolving tablets of pioglitazone hydrochloride prepared by solid dispersions of drug with PEG 4000 and combination of diluents and cross povidone as super disintegrant provide complete and better dissolution within in shorter period of time. Hence effective diabetic treatment anywhere, and at anytime particularly for geriatric, pediatric, mentally ill, bedridden and patients who do not have easy access to water can be done.

KEYWORDS *Pioglitazone hydrochloride, PEG 4000, cross povidone, SSG, solid dispersion, fast dissolving tablets.*

INTRODUCTION

Pioglitazone hydrochloride is an oral hypoglycemic agent, which is a commonly prescribed drug for the treatment of patients with type II diabetes mellitus. Pioglitazone hydrochloride is a basic (pKa = 12.06) which is practically insoluble in water and alkaline buffer solutions, but as per the Biopharmaceutical Classification System (BCS) Pioglitazone categorized as class II drug. The oral absorption is uniform, rapid and complete with a bioavailability of nearly 100% and an elimination half-life of 3-7 hrs. Formulations for Pioglitazone hydrochloride for better control of blood glucose levels to prevent hypoglycemia enhance clinical efficacy and patient compliance. One such approach is or dispersible tablet. Oral routes of drug ne such approach is or dispersible tablet. Oral routes of drug administration have wide acceptance up to 5060% of total dosage forms. Solid dosage forms are popular because of ease of administration, accurate dosage, self-medication, pain avoidance and most importantly the patient compliance.

Pioglitazone is a prescription drug of the class thiazolidinedione with hypoglycemic (antihyperglycemic, antidiabetic) action. Pioglitazone HCL reduces insulin resistance in the liver and peripheral tissues; increases the expense of insulin-dependent glucose; decreases withdrawal of glucose from the liver; reduces quantity of glucose, insulin and glycated haemoglobin in the bloodstream. Following oral administration, in the fasting state, Pioglitazone HCL is first measurable in serum within 30 minutes, with peak concentrations observed within 2 hours. Food slightly delays the time to peak serum concentration to 3 to 4 hours, but does not alter the extent of absorption. Mouth dissolving tablets are also called as fast dissolving tablets, melt-in mouth tablets, Orodispersible tablets, rapid melts, porous tablets, quick dissolving etc. Mouth dissolving tablets are those when put on tongue disintegrate instantaneously releasing the drug which dissolves or disperses in the saliva the faster the drug into solution, quicker the absorption and onset of clinical effect. Some drugs are absorbed from the mouth, Pharynxand esophagus as the saliva passes down into the stomach. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablets dosage form.

Material and Methods

Pioglitazone hcl was purchased from OASIS Laboratories Pvt. Ltd. Jaipur. The super disintegrant SSG, PEG and CCS was purchased from the same laboratory. The other excipients were bought from the laboratory of our known place.

Preparation of stock solutions:

An accurately weighed 10.0 mg of pure drug Pioglitazone hydrochloride was taken in clean, dry 100 ml volumetric flask and dissolved in small volume of Methanol (10.0 – 20.0 ml). The solution was diluted to 100.0 ml with Methanol, resulting in 100.0 mcg/ml of drug concentration.

Selection of analytical concentration range: Aliquots of 0.2 ml, 0.4 ml, 0.6 ml, 0.8 ml, 1.0 ml, 1.2 ml, & 1.4 ml of 100 µg/ml of Pioglitazone Hydrochloride were pipetted into six 10 ml volumetric flask The volume were made up to 10 ml with Methanol was measured at 248 nm against methanol as a blank. For standard solution analytical concentration range was found to be 02-12 µg/ml and overlain spectra was obtained.

Preparation of Calibration Curve

Aliquots of 2, 4, 6, 8, 10, 12 µg/ml solution of Pioglitazone Hydrochloride was pippetted from stock solution into each of five 10 ml of volumetric flask. The volume was made up to 10.0 ml with Methanol. The absorbance of the solution was measured at 248 nm against Methanol as blank. The absorbance values are recorded in Table No. 2 and represented graphically in Fig No. 2.

10 mg of Pioglitazone Hydrochloride was weighed accurately and dissolved 5 ml methanol in a 100 ml of volumetric flask and volume was made up to 100 ml. The calibration curve was plotted between concentration and absorbance.

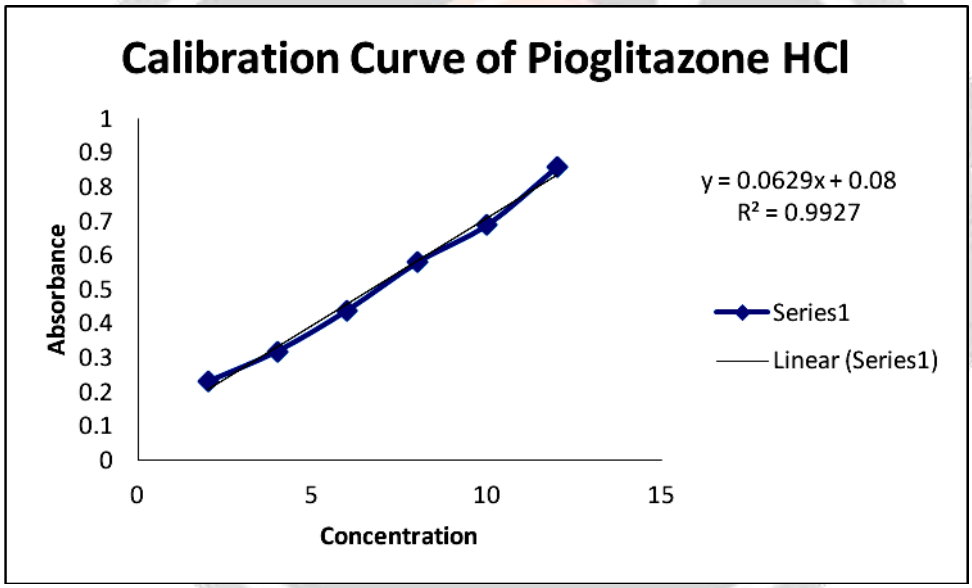


Fig.1: Preparation of Standard Curve of Pioglitazone Hydrochloride in Methanol

Preparation of solid dispersion of Pioglitazone Hydrochloride

1.1 Preparation of physical mixture

Physical mixture (PM) of Pioglitazone Hydrochloride was prepared by mixing accurately weighed amounts of PGH with carrier's viz. PEG 4000 in proportion of 1:1, 1:2, 1:3 and 1:4 by with the help of a spatula for 10 minutes.

1.2 Preparation of Solid Dispersion (SD) of Pioglitazone Hydrochloride

Solid dispersion is one of the most commonly used techniques to improve the solubility of water insoluble drugs which in turn improves the bioavailability. The SD of Pioglitazone Hydrochloride was prepared by conventional solvent evaporation method using PEG 4000 as carrier. Solid dispersion formulations were prepared using different ratios of drug and carrier i.e. 1:1, 1:2: 1:3 and 1:4. Different amount of PEG 4000 such as 1, 2, 3 and 4 gm were separately dissolved in ethanol, while 1 gm PGH was dissolved in the solution with the ratio of drug to carrier as 1:1, 1:2, 1:3 and 1:4 (w/w). The solvent was evaporated on a heating mantle maintained at 45± 2^{o}C. The samples were dried in a desicator for 24 hrs calcium chloride. Dried mass was scrapped, crushed, pulverized and passed through over anhydrous sieve (#100). The best ratio of PEG 4000 with PGH was chosen via dissolution tests. The ratio and assigned batch code are given in table 3.3.3.

1.3 Preparation of drug free tablets

Drug free fast dissolving tablets were prepared by Slugging method using single punch Cadmach tablet machine. The formulations were developed by using different excipients and superdisintegrents in various ratios.

1.4 By addition of super disintegrates

Drug free fast dissolving tablets were prepared by Slugging method using 10 station punch shakti pharmatech machine. All the superdisintegrants (Sodium starch glycolate, Crospovidone and Crosscarmellose sodium in different ratio as 2%, 4%, 6% and 8% respectively) and excipients were weighted accurately and make slug and developed the granules via passing the slug through #100 and dried in autoclave at a temperature about 45^{o}C. Then these granules were 10 stations punch using Shakti Pharmatech machine produced 320 mg of each tablets respectively.

Table: 1 Formulation of fast dissolving drug free tablet (Wt. in mg each tablet)

Ingredients	P1	P2	P3	P4
SodiumStarch Glycolate	6.4	12.8	19.2	25.6
Avicel pH 102	98	96	94	92
Lactose	65	63	61	59
Sorbitol	50.6	49.2	47.8	46.4
Mannitol	94	93	92	91
Talc	2	2	2	2
Magnesium Stearate	4	4	4	4

Table: 2 Formulation of fast dissolving drug free tablet (Wt. in mg each tablet)

Ingredients	P5	P6	P7	P8
Crospovidone	6.4	12.8	19.2	25.6
Avicel pH 102	98	96	94	92
Lactose	65	63	61	59
Sorbitol	50.6	49.2	47.8	46.4
Mannitol	94	93	92	91
Talc	2	2	2	2
Magnesium Stearate	4	4	4	4

2.1 ANALYSIS OF PIOGLITAZONE HCL

1. Differential Scanning Calorimetry (DSC)

Differential Scanning Calorimetry (DSC) measurements were performed using Differential scanning calorimeter equipped with a liquid nitrogen sub-ambient accessory. The instrument operated under nitrogen purge gas at a rate of 20 ml/min. The samples were examined at a heating rate of 10^{o} C/ min from 30^{o} C to 300^{o}C in nitrogen atmosphere. Accurately weighted amounts of samples were placed in perforated aluminium pans. Indium was used to calibrate for the temperature scale and energy. Differential Scanning Calorimetry (DSC) was employed to determine the melting point of Pioglitazone HCL sample used in present investigation.

2. Fourier Transform Infrared Spectroscopy (FTIR)

The IR analysis of the sample was carried out for qualitative compound identification, used to record IR spectra of the prepared discs, to confirm any interaction of Pioglitazone HCL with other excipients of dispersion. The pellet of approximately 01 mm diameter of the drug was prepared grinding 3-5 mg of sample with 100-150 mg of Potassium Bromide (KBr) in pressure compression machine. The procedure consisted of dispersing a sample (drug alone or mixture of drug and excipients) in KBr and compressing into discs by applying a pressure. The pellet was placed in the light path and the spectrum was obtained. The sample pellet was mounted in IR compartment and scanned at wavelength 4000 cm^{-1} – 400 cm^{-1}.

3. Ultraviolet Spectroscopy

Ultraviolet spectroscopy analysis of drug was carried out for wavelength maxima and absorbance determination and calibration of standard curve of drug. This was done by forming various conc. of solution (0-26 mcg/ml) of drug and run the spectroscopy in the rage 200 to 400 nm to obtained the absorbance for their relative concentration was measured.

4. Solubility Determination

Solubility Determination was performed according to Higuchi and Connors. The solubility of Pioglitazone HCL was determined in different solvents. An excess quantity of the drug was added in 10 ml of each solvent in screw capped glass test tubes and shaken or 24 hours at room temperature. The solution was filtered, diluted and the solubility was determined by Double beam spectrophotometer Systronics at 248 nm.

5. Partition coefficient

The partition coefficient of Pioglitazone HCL was determined in n-octanol: sorensons buffer system. An accurately weighed (500 mg) amount of Pioglitazone HCL was added into 10 ml each of n-octanol and aqueous phase in a screw capped tube. The mixture was shaken for 24 hours until equilibrium was reached. Phases were separated; the aqueous phase was filtered, diluted and the amount of Pioglitazone HCL solubilized in aqueous phase was determined by measuring the absorbance at 248 nm spectrophotometrically.

The partition coefficient of Pioglitazone HCL was calculated from the ratio between the concentration of Pioglitazone HCL in organic and aqueous phase using following equation:

$P_{o/w} = (C_{Oil} / C_{pH\ 6.8})$ equilibrium

Table 3: Determination of Absorption Maxima of Pioglitazone Hydrochloride in Methanol.

S.N.	Wavelength	Absorbance
1	238	2.271
2	244	2.278
3	248	2.412
4	250	2.314
5	252	2.124

Fig.2: Determination of Absorption Maxima of PGH in Methanol

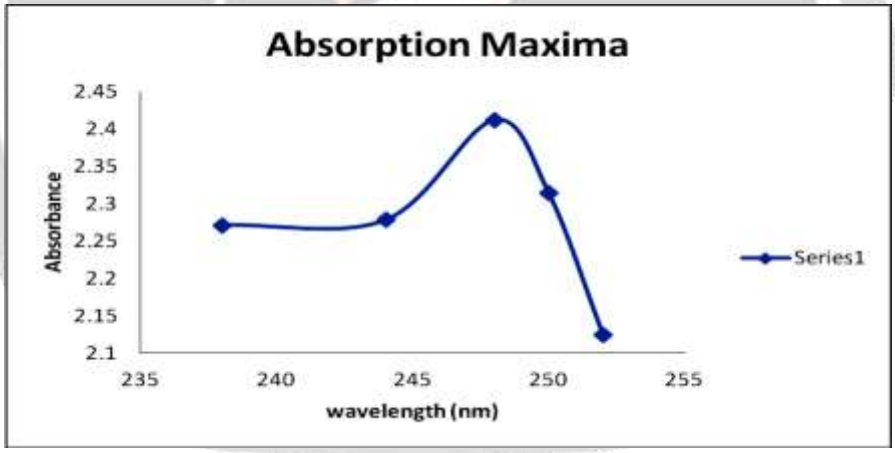


Table: 4 Pioglitazone Hydrochloride FDT by Addition of Super disintegrates

Ingredients	PGHT1	PGHT2	PGHT3	PGHT4	PGHT5	PGHT6
Pioglitazone Hydrochloride	30	30	30	30	30	30
SSG	12.8	19.2	-	-	-	-
CP	-	-	12.8	19.2	-	-
CCS	-	-	-	-	12.8	19.2
Avicel pH 102	90	88	90	88	90	88
Lactose	53	50	53	50	53	51

Sorbitol	**39.6**	**38.2**	**39.6**	**38.2**	**39.6**	**38.2**
Mannitol	**85**	**86**	**85**	**86**	**86**	**85**
Talc	**3.6**	**2.6**	**3.6**	**2.6**	**2.6**	**2.6**
Magnesium stearate	**6**	**6**	**6**	**6**	**6**	**6**
Total wt. (mg)	**320**	**320**	**320**	**320**	**320**	**320**

Table :5 Pioglitazone Fast Dissolving Tablets by Solid Dispersion technology

Ingredients	PGHT7	PGHT8	PGHT9	PGHT10	PGHT11	PGHT12
Pioglitazone Hydrochloride + PEG 4000 (1:4)	**1050**	**150**	**150**	**150**	**150**	**150**
SSG	**12.8**	**19.2**				
CP	**-**	**-**	**12.8**	**19.2**	**-**	**-**
CCS	**-**	**-**	**-**	**-**	**12.8**	**19.2**
Avicel pH 102	**42**	**41**	**43**	**41**	**42**	**39**
Lactose	**55**	**54**	**55**	**54**	**55**	**54**
Sorbitol	**12.2**	**10.8**	**12.2**	**10.8**	**12.2**	**10.8**
Mannitol	**42**	**39**	**41**	**39**	**42**	**41**
Talc	**3**	**3**	**3**	**3**	**3**	**3**
Magnesium stearate	**3**	**3**	**3**	**3**	**3**	**3**
Total wt. (mg)	**320**	**320**	**320**	**320**	**320**	**320**

2.2 Characterization of Solid dispersions

Saturation Solubility Determination

Solubility Determination was performed according to Higuchi and Connors. The saturation solubility of drug (PGH), physical mixtures and SDs with PEG 4000 (1:1, 1:2, 1:3 and 1:4 w/w) was determined by adding an excess amount of drug (10 mg), physical mixture and SDs to 50 ml aqueous solution of water soluble carrier (PEG 4000) in various ratio such as 1:1, 1:2, 1:3 and 1:4 in screw capped bottles. Samples were shaken for 24 hrs at room temperature. Subsequently, the suspensions were filtered through a whatmann filter paper no. 1. Then the filtered solution diluted properly with methanol. The diluted solution analysed for the PGH in Double beam spectrophotometer 2203 (SYSTRONICS) at 248nm.

Fourier Transform Infrared Spectroscopy (FTIR)

The KBr discs of PGH, PEG 4000 and finalized solid dispersion were prepared (2 mg sample in 200 mg KBr) using electrically operated KBr press model SHIMADZU FTIR-5300 fourier transform spectrophotometer was used to record IR spectra of the prepared discs, to confirm any interaction of Pioglitazone with other excipients of dispersion. The procedure consisted of dispersing a sample (drug alone or mixture of drug and excipients) in KBr and compressing into discs by applying a pressure. The pellet was placed in the light path and the spectrum was obtained. The sample pellet was mounted in IR compartment and scanned at wavelength 4000 cm^{-1} – 400 cm^{-1}.

Differential Scanning Calorimetry (DSC)

Differential Scanning Calorimetry (DSC) measurements were performed on Pioglitazone, PEG 4000 and its solid dispersion formulation using Differential scanning calorimeter equipped with a liquid nitrogen sub-ambient accessory. The instrument operated under nitrogen purge gas at a rate of 20 ml/min. The samples were examined at a heating rate of 10^{o} C/ min from 30^{o} C to 250^{o}C in nitrogen atmosphere. Accurately weighted amounts of samples were placed in perforated aluminium pans. Indium was used to calibrate for the temperature scale and energy.

Scanning Electron microscope studies (SEM)

The surface morphology of the layered sample was examined by using SEM. The Solid dispersion was examined by Scanning electron microscope to investigate the surface morphology and homogeneity of the particles. The small amount of powder was manually dispersed onto a carbon tab (double adhesive carbon coated tape) adhered to an aluminum stubs. These sample stubs were coated with a thin layer (30Å) of gold by employing POLARON-E 3000 sputter coater at room temperature before examination to render the surface of particles electro-conductive. The

scanning range was 450 to 4,000 cm^{-1} and the resolution was 1 cm^{-1}. The samples were examined by SEM and photographed under various magnifications with direct data capture of the images onto a computer.

Drug content analysis

The drug content in each solid dispersion and physical mixture was determined by the UV-Spectroscopic method. An accurately weighed quantity of solid dispersion or physical mixture, equivalent to 30 mg of Pioglitazone, was transferred to a 100 ml volumetric flask containing 10 ml of methanol and dissolved. The volume was made up to 100 ml.The solution was filtered and the absorbance was measured after suitable dilutions by using Double beam spectrophotometer 2203 (SYSTRONICS) at 248nm.

In Vitro dissolution studies of solid dispersion

In-vitro Dissolution of Pioglitazone solid dispersions were studied in Dissolution test apparatus LAB INDIA DS8000. 900 ml .The temperature of 37 ± 0.5° C was maintained throughout the experiment Solid products, solid dispersions as well as physical mixtures, each containing 30 mg of drug were subjected to dissolution. At fixed time intervals, 5 ml samples withdrawn were filtered and spectrophotometrically analyzed for the drug content at 248 nm. The volume withdrawn at each interval was replaced with fresh quantity of dissolution medium. The amount of Pioglitazone released was calculated and plotted against time.

2.3 Evaluation of Pioglitazone Hcl Fast Dissolving Tablets:

The tablets after punching of every batch were evaluated for in-process and finished product quality control tests i.e. pre-compression parameters and post-compression parameters.

Pre-compression studies (Evaluations of blends)

The evaluations of pre-compression studies of formulated Fast dissolving tablets of Pioglitazone were done as per standard procedure. The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. There are many formulation and process variables involved in mixing step and all these can affect the characteristics of blends produced.

The following parameters were evaluated.

Bulk density:

Density is defined as weight per unit volume. Bulk density, ρ_b, is defined as the mass of the powder divided by the bulk volume and is expressed as gm/ cm^3.The bulk density of a powder primarily depends on particle size distribution, particle shape and the tendency of particles to adhere together. There are two types of bulk density.

Low bulk density: The particles are pack in such a way so as to leave large gaps between their surfaces resulting up in light powder of low bulk density.

High bulk density: Here the smaller particles shift between the large particles resulting in heavy powder of high bulk density.

Bulk density is very important in the size of containers needed for handling, shipping, and storage of raw material and blend. It is also important in size blending equipment.

A standard procedure used for obtaining bulk density or its reciprocal bulkiness is given below

A sample of about 50 cm^3 (blend) is carefully introduced in a 100ml graduated cylinder. The cylinder is dropped onto a hard wood surface three times from a height of 1 inch at two second interval. The bulk density is then obtained by dividing the weight of sample in gms by final volume in cm^3.

The bulk density is calculated by given formula,

Bulk density (B_d) = Mass of the powder (M) / Bulk volume (V_B)

Tapped density:

It is the ratio of total mass of powder to the tapped volume of powder. The volume was measured was measured by tapping the powder for 500 times. It is expressed by given formula,

Tapped density (T_d) = Mass of the powder (M) / Tapped volume (V_T)

Carr's index or % compressibility:

It indicates powder flow properties. It is the simple test to evaluate the bulk density and tapped density of a powder and the rate at which it packed down. It is expressed in percentage and is given by

% Compressibility (% I) = $T_d - B_d / T_d \times 100$

Where, T_d and B_d are tapped density and bulk density respectively.

Table:6 Specification of Carr's index for granules as per I.P

S. No.	Carr's index (%)	Types of flow
1.	5-10	Excellent
2.	12-16	Good
3.	18-23	Fair to possible
4.	23-35	Poor

5.	**33-38**	**Very poor**
6.	**Above 40**	**Extremely poor**

Hausner Ratio:

Hausner ratio is an indirect index of ease of powder flow. It is the ratio of tapped density to the bulk density. It was calculated by the following formula,

Hausner ratio = T_d / B_d

Where, T_d and B_d are tapped density and bulk density respectively.

The ideal range of Hausner ratio should be 1.2-1.5.

Angle of Repose:

The frictional force in a loose powder can be measured by the angle of repose θ. It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. The angle of repose was determined by the funnel method suggested by Newman. For determination of angle of repose (θ), the blend were poured through the walls of a funnel, which was fixed at a position such that its lower tip was at a height of exactly 2.0 cm above hard surface. The blends were poured till the time when upper tip of the pile surface touched the lower tip of the funnel. Angle of repose was calculated using following equation.

$\tan\theta = (h/r)$

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

Where θ = Angle of repose; h = height of pile; r = radius of pile

Table:7: Specification of Angle of repose for granules as per IP

S. No.	Angle of repose (degree)	Types of flow
1.	**Less than 25**	**Excellent**
2.	**25-30**	**Good**
3.	**30-40**	**Possible**
4.	**Above 40**	**Very poor**

***In-vitro* Drug Release:**

In-vitro drug release rates from different tablets prepared from solid dispersion were determined in 900 ml in dissolution media, maintained at 37 ± 0.5^0C with a stirrer rotation speed of 50 rpm using the Dissolution test apparatus LAB INDIA DS8000. 5 ml sample of dissolution medium was withdrawn at 5, 10, 15, 20, 25, 30 minutes using a cannula and syringe. The sample filtered through whatmann filter paper and suitably diluted and assayed spectrophotometrically at 248 nm. An equal volume of fresh medium, which was prewarmed at 37^0 C was replaced into the dissolution medium after each sampling to maintain the constant volume throughout the test. Each dissolution rate test was repeated three times.

The various kinetic treatments were given to the dissolution data. The in vitro permeation data obtained were subjected to a zero order and first order kinetics, Korsemeyer's equation, Higuchi model to understand the release profile and release mechanism. When a graph of the cumulative percentage of the drug released from the tablet against time is plotted, zero order release is linear in such a plot, indicating that the release rate is independent of concentration.

3. RESULT AND DISCUSSION

In the present study, fast dissolving tablets of Pioglitazone Hcl were prepared and evaluated for their use to obtain fast release and to prevent first pass metabolism.

3.1 Analytical Profile of Pioglitazone Hcl:

DSC studies

DSC Studies were used to characterize the physical state of drug in various formulations. Thermogram of pure Pioglitazone HCl and optimized formulation were shown in the Figures below. Pure Pioglitazone HCl shows single sharp endotherm at 176^0C, which corresponds to the melting point. The decrease in melting point in optimized formulation indicated that decrease in crystallinity.

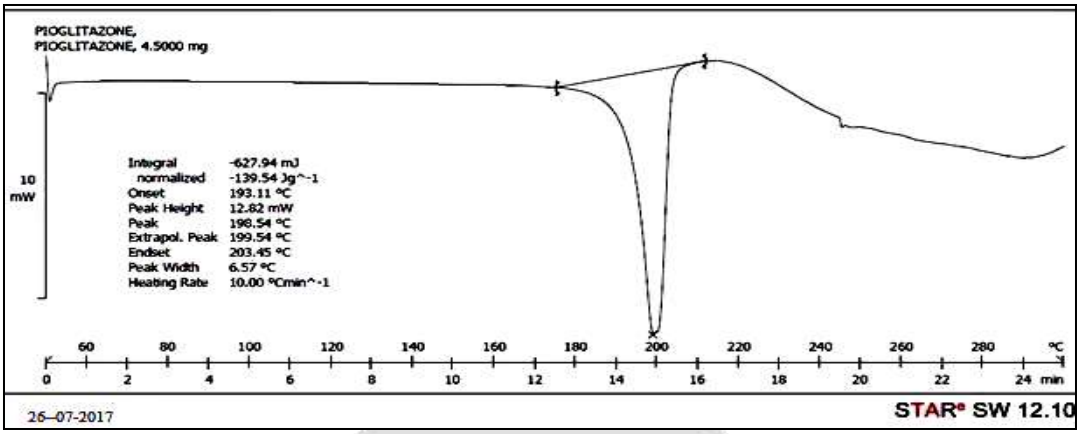


Fig: 3 DSc Graph:

FTIR STUDIES: FTIR Studies were conducted to determine the possible interactions between drug and excipients. FTIR Spectra of pure Pioglitazone HCl and drug with excipients show no chemical interaction drug and excipients. The FTIR Spectra were shown in Figures 2 to 6. the characteristic peak of 720cm-1,1241cm-1, 1743cm-1, 2900cm-1, 3085cm-1 and 3400cm-1 which correspond to H-H stretching, C-H stretching [aliphatic], C=O stretching, C-O linkage and CH2 group out of the plan respectively.

Physical mixture of the drug and PEG 4000 shows summation of the spectra of the drug and PEG 4000 equivalent to the addition of the spectrum of polymer and drug. This indicates that interaction has occurred with simple physical mixture of drug and polymer. In case of solid dispersion of the drug and PEG shows overlapping of O-H and N-H group and broadening of the peak was observed. At the same time peak has shifted toward the higher wavelength 3411.84 may be due to the presence of more number of O-H groups in PEG.. This indicates that overall symmetry of the molecule might not be significantly changed. From the FTIR study it was found that some of the peaks of the drugs were shifted broadened, some present with reduced intensity and some vanished. This was referred to formation of a complex between the drug and carrier. Complexation was leading to formation of an amorphous form of drug with PEG 4000 by SD leading to improve the dissolution rate of drug.The drug and superdisintegrants spectra also indicate overall symmetry of the molecule might not be significantly changed.

Fig: 4 FTIR Graph Pure Drug

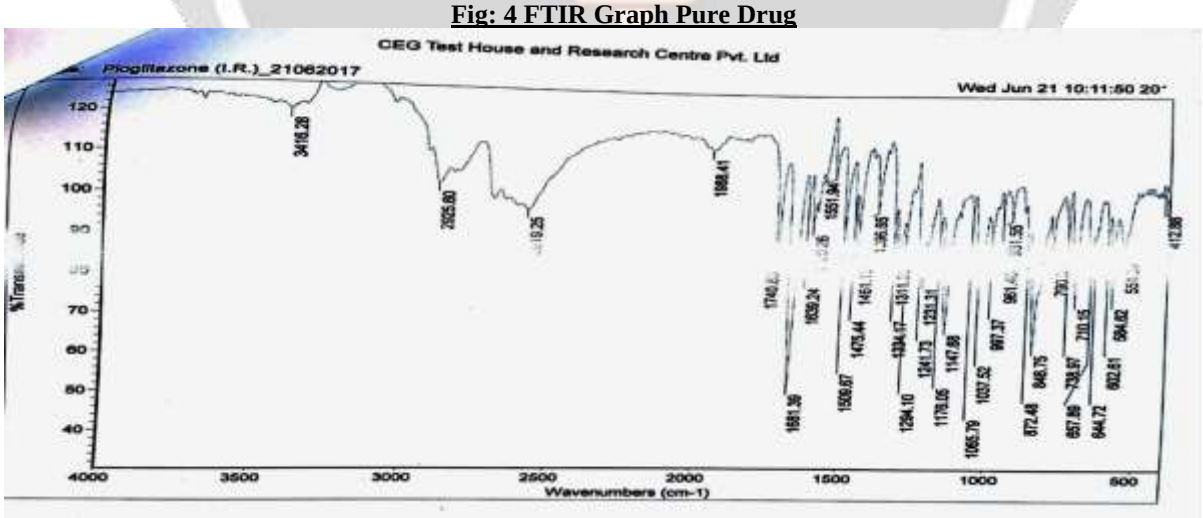
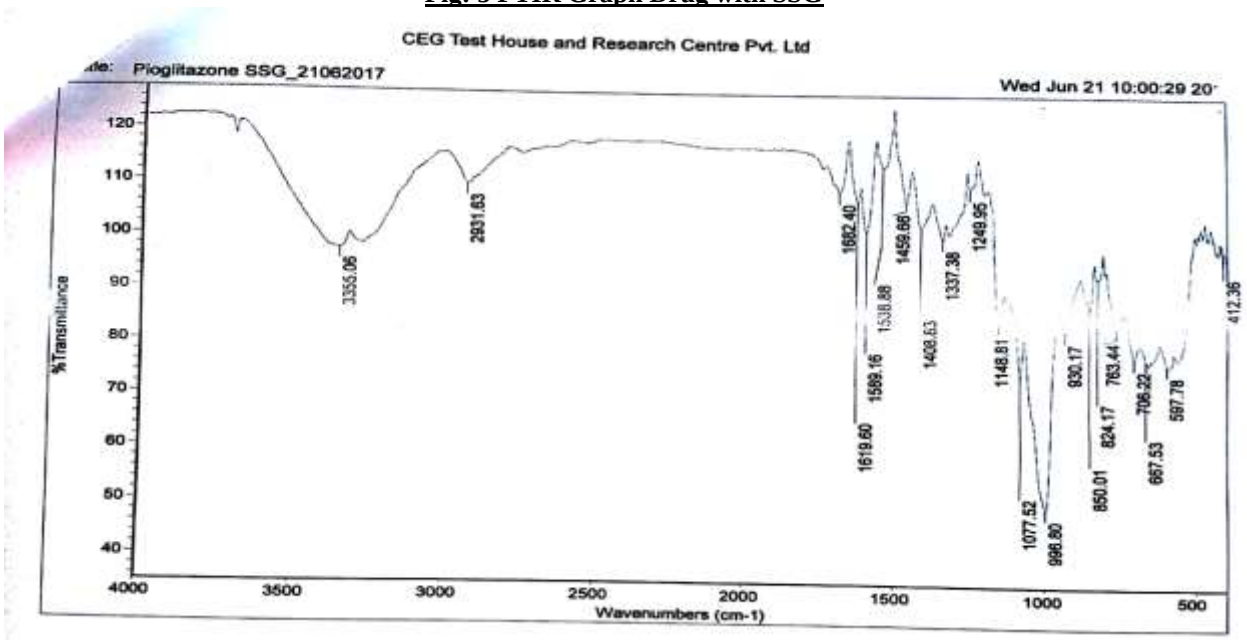


Fig: 5 FTIR Graph Drug with SSG



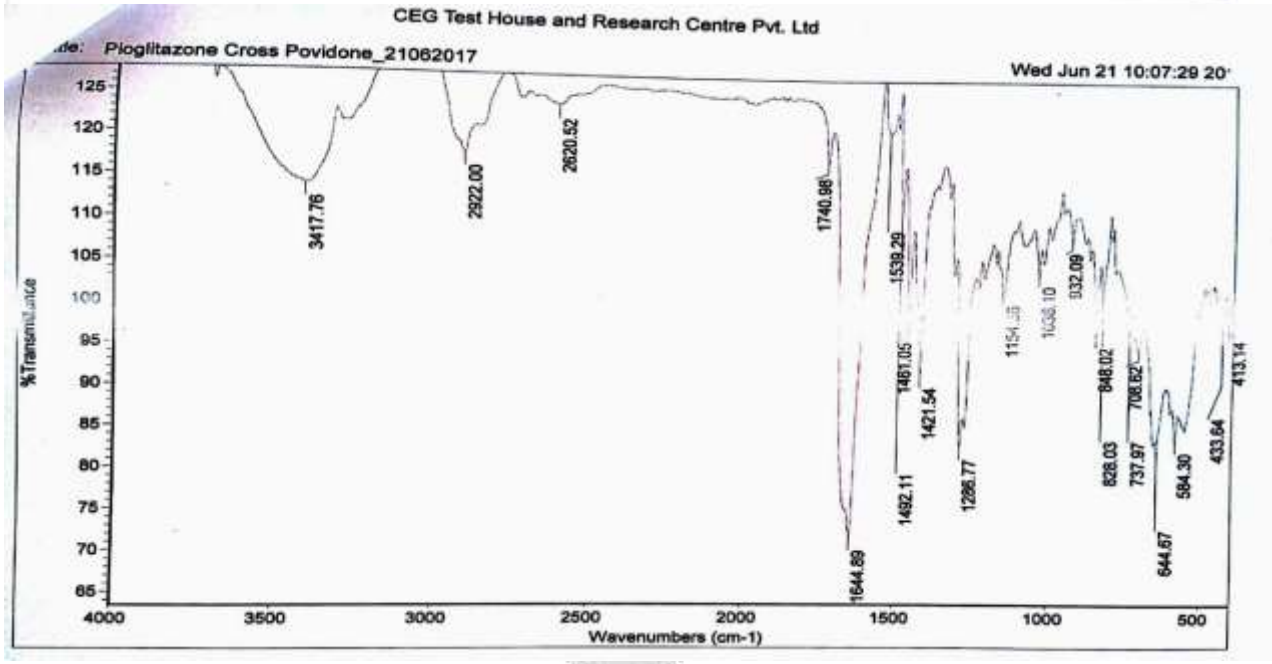


Fig: 6 FTIR Graph Drug with Cross povidone

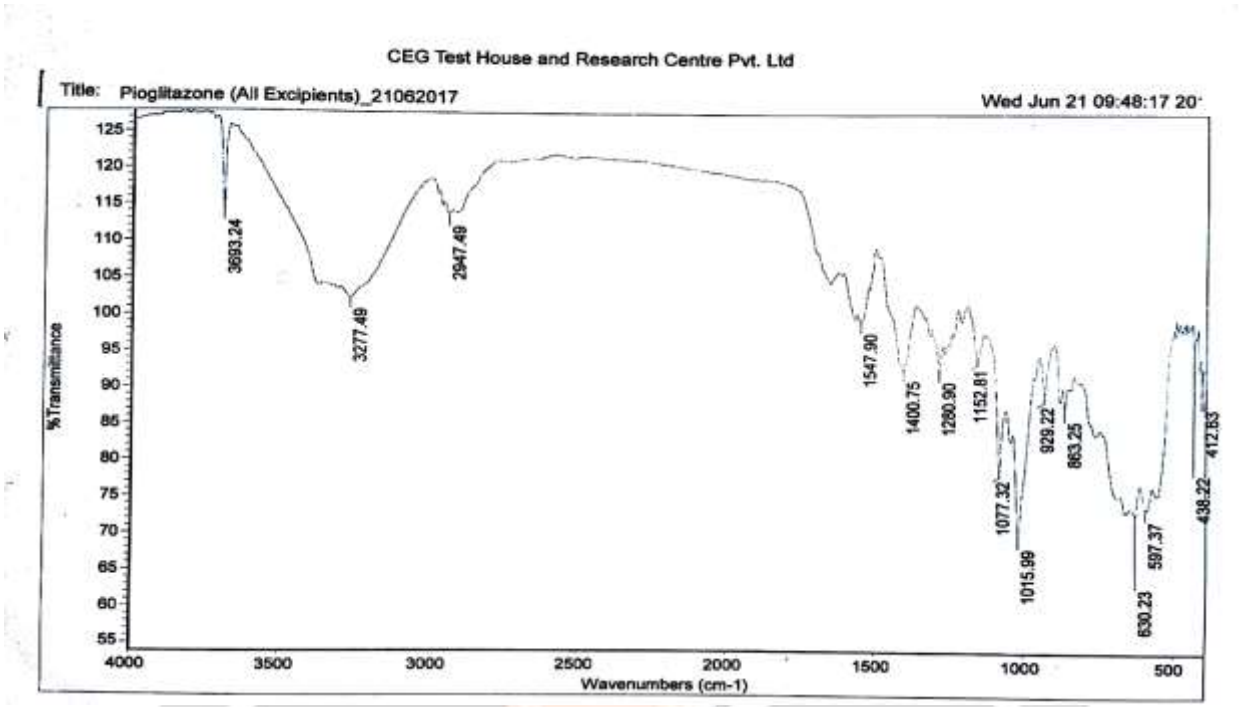


Fig: 7 FTIR Graph Drug with all excipients

PGHT8>PGHT10>PGHT7>PGHT12>PGHT9>PGHT2>PGHT11>PGHT4>PGHT1>PGHT3>PGHT6>PGHT5
Formulations PGHT1, PGHT2, PGHT3, PGHT4, PGHT5 and PGHT6 which contain 4 and 6 % superdisintegrant (Sodium starch glycolate, Crospovidone and Crosscarmellose sodium respectively). The release found to be at the end of five minutes 88.671, 91.063, 84.786, 89.323, 81.272, 83.567 respectively. The formulations with SSG shows more release than the tablets with Crospovidone and CCS. An increase in the drug release was observed when the drug used as solid dispersion with PEG 4000 in ratio of 1:4. The formulations contain solid dispersion PGHT7, PGHT8, PGHT9, PGHT10, PGHT11, PGHT12 with equal concentration of disintegrant as 4 and 6 % SSG, CP and CCS respectively.
This signifies that solid dispersion and the ratio of Pioglitazone: PEG 4000 (1:4) is the best ratio for the enhancement of solubility of water insoluble Pioglitazone and sufficient for the formulation of fast dissolving tablets of Pioglitazone Hcl.

Table 8: Fit of Various Kinetic Models for Fast Dissolving Tablet of Pioglitazone Hcl

Formulation code	Zero Order R^2	First Order R^2	Higuchi Model R^2	Korsemeyer Model R^2
PGHT1	**0.842**	**0.980**	**0.943**	**0.959**
PGHT2	**0.808**	**0.977**	**0.922**	**0.950**
PGHT3	**0.876**	**0.986**	**0.964**	**0.975**
PGHT4	**0.825**	**0.975**	**0.926**	**0.945**
PGHT5	**0.894**	**0.986**	**0.973**	**0.978**
PGHT6	**0.826**	**0.958**	**0.919**	**0.932**
PGHT7	**0.774**	**0.971**	**0.916**	**0.954**
PGHT8	**0.727**	**0.962**	**0.894**	**0.945**
PGHT9	**0.795**	**0.971**	**0.926**	**0.955**
PGHT10	**0.756**	**0.970**	**0.906**	**0.967**
PGHT11	**0.871**	**0.976**	**0.979**	**0.900**
PGHT12	**0.790**	**0.970**	**0.925**	**0.953**

CONCLUSION

In the present study pioglitazone solid dispersion was prepared by different methods using PEG4000 as a hydrophilic carrier in different ratios. The pioglitazone solid dispersion prepared by using PEG4000 as a hydrophilic

carrier in a ratio of 1:4 can be successfully used to improve its dissolution as indicated by in vitro dissolution studies. This solid dispersion was further formulated as FDTs using SSG and CCS as superdisintegrants, mannitol and avicel as diluents in order to gain better patient compliance and effective therapy. Tablets thickness, hardness, friability, disintegration time and in vitro release studies were evaluated for the prepared tablets.The formulations with SSG showed more release than the tablets with Crospovidone and CCS. An increase in the drug release was observed when the drug used as solid dispersion with PEG 4000 in ratio of 1:4.

REFERENCES:

[1]. Shamir R., A. Lerner, and E. A. Fisher. "Hypercholesterolemia in Children." Israel Medical Association Journal 2, no. 10 (2000): 767-771.

[2]. Davidson MH: Rosuvastatin: a highly efficacious statin for the treatment of dyslipidaemia. Expert Opin Investig Drugs. 2002 Mar; 11(3):125-41.

[3]. Braunwald, Eugene, Douglas Zipes, and Perter Libby. Heart Disease: A Textbook of Cardiovascular Medicine. 6th ed. Philadelphia: Saunders, 2001.

[4]. Foody, J.M, and Eugene Braunwald. Preventive Cardiology: Strategies for the Prevention and Treatment of Coronary Artery Disease. Totowa, NJ: Humana Press, 2001.

[5]. Hiatt, William R. "Atherosclerotic peripheral arterial disease." In Cecil Textbook of Medicine, edited by Lee Goldman and J. Claude Bennett, 21st ed. Philadelphia: W.B. Saunders, 2000, pp. 357-362.

[6]. Chauvin B, Drouot S, Barrail-Tran A, Taburet AM: Drug-Drug Interactions Between HMG-CoA Reductase Inhibitors (Statins) and Antiviral Protease Inhibitors. Clin Pharmacokinet. 2013 May 24.

[7]. Neuvonen PJ, Niemi M, Backman JT: Drug interactions with lipid-lowering drugs: mechanisms and clinical relevance. Clin Pharmacol Ther. 2006 Dec; 80(6):565-81.

[8]. Mechcatie, Elizabeth. "FDA Okays Rosuvastatin for Hypercholeterolemia: Most Potent Statin to Date." Internal Medicine News September 1, 2003: 30-31.

[9]. More S., Ghadge T. "Fast disintegrating tablets: An overview". *Asian Journal of Research Pharm. Sci.* 2013; 3(2): 47-55.

[10]. Pahwa R, Piplani M, Prabodh C, Kaushik D and Nanda S; Orally Disintegrating Tablets-Friendly to Paediatrics and Geriatrics; Available online at www.scholarsresearchlibrary.com.

[11]. Kaur T, Gill B, Kumar S et al. Mouth dissolving tablets: A novel approach to drug delivery. International Journal of Current Pharm Res. 2011; 3(1):3-7.

[12]. Hamilton EL, Luts EM. Advanced Orally disintegrating tablets bring significant benefits to patients and product life cycle. Drug Delivery Technol. 2005; 5(1):34-7.

[13]. Arya A, Chandra A. Fast drug delivery systems: A review. Der pharmacialetter 2010; 2(2):350-61.

[14]. Agrawal VA, Rajurkar RM. Fast disintegrating tablet as a new drug delivery system:A review. International Research Journal Pharmacophore. 2011; 2(1):1-8

[15]. Velmurugan S, Vinushitha S. Oral disintegrating tablets: An overview. International Journal Chem Pharma Sci. 2010; 1(2):1-12.

[16]. Corveleyn S. and Remon JP. Freeze-Dried Disintegrating Tablets. US patent no. US6 010719. 2000.

[17]. Debjit B, Chiranjib B. Fast dissolving tablet: An overview. Journal of Chemical and Pharmaceutical Research. 2009; 1(1):163-77.

[18]. Divate S, Kunchu K. Fast disintegrating tablets-an emerging trend. International Journal of Pharmaceutical Sciences Review and Research 2011; 6(2):18-22.

[19]. Ghadge S, Keskar S, Oral disintegrating tablets: An overview International Journal of Universal Pharmacy and Life. 2011; 4(2):5-9

[20]. Ashish P, Harsoliya MS, Pathan JK, Shruti S. A Review-Formulation of mouth dissolving tablet. International Journal of Pharma Clinical and Science. 2011; 1(1):1-8.

[21]. Seager H. Drug-deliver Products and the Zydis Fast-dissolving Dosage Form. Journal of Pharm. and Pharmacol. 1998; 50: 375-82.

[22]. Pather SI, Khankari RK, Moe DV. OraSolv and DuraSolv: Efficient technologies for the production of orally disintegrating tablets. Drugs and the Pharmaceutical Sciences. 2003; 2(6): 203-16.

[23]. Gupta A, Mishra A M, Gupta V. Recent Trends of Fast Dissolving Tablet-An Overview of Formulation Technology. International Journal of Pharma& Biological Archives: 2010;1(1):59-65.

[24]. Yamanouchi Pharma Technologies, Inc. WOWTAB. 25 JAN 2011; Available at:http://www.ypharma.com/wowtab.html.

[25]. Reddy D, Pillay V, Choonara YE, Du-Toit LC. Rapidly disintegrating oramucosal drug delivery technologies. Pharmaceutical development and technology. 2009; 14(6); 588-601.

[26]. Www. ElanNanoCrystal_Technology.html.
[27]. Mizumoto T, Masuda Y, Yamamoto T, Yonemochi E, Terada K. Formulation design of a novel fast disintegrating tablet. International journal of Pharmaceutics. 2005; 306(1-2):83-90.
[28]. Bhupendra G Prajapati et al; A Review on Recent patents on Fast Dissolving Drug Delivery System; International Journal of Pharma Tech Research (IJPRIF). 2009; 1(3): 790-98.
[29]. http://www.drugbank.ca/drugs/DB01076
[30]. http://www.rxlist.com
[31]. Jacobsen W, Kuhn B, Soldner A, Kirchner G, Sewing KF, Kollman PA, Benet LZ, Christians U: Lactonization is the critical first step in the disposition of the 3-hydroxy-3-methylglutaryl-CoA reductase inhibitor atorvastatin. Drug Metab Dispos. 2000 Nov; 28(11):1369-78.
[32]. Jafari M, Ebrahimi R, Ahmadi-Kashani M, Balian H, Bashir M: Efficacy of alternate-day dosing versus daily dosing of atorvastatin. J Cardiovasc Pharmacol Ther. 2003 Jun; 8(2):123-6.
[33]. Kibbe AH, "Handbook of Pharmaceutical Excipients", London and Washington, DC: Pharmaceutical Press and American Pharmaceutical Association, 2000; Ed. 3: 642–643.
[34]. Marishita M, Goto T, Peppas NA, "Excipients and pharmaceutical medicine", J Control Release, 2004; 97(1): 67-78.
[35]. Marcel T, Nerenbaum L, "Sodium starch glycolate-Excipients and disintegration behaviour of drugs", Int. J. Pharm., 2004; 277(1-2): 91-97.
[36]. Fiegel J, Fu H, Hanes J., "release modifier: handbook of pharmaceutical excipients", J. Control Release, 2004; 96(3): 411–423.
[37]. Habib W, Khankari R, Hontz J. Fast-dissolving Drug Delivery Systems: Critical Reviews ™Therapeutic Drug Carrier Systems. 2000; 17(1):61-72.
[38]. Anand V, Kataria M., Kukkar V, Saharan V, Choudhury P, "The Latest Trends In the Taste Assessment of Pharmaceuticals," Drug Discovery Today, March 2007; 12: 257-65.
[39]. Szejtli J, Szente L. Elimination of Bitter, Disgusting Tastes of Drugs and Foods by Cyclodextrins. European Journal of Pharma. Biopharm. 2005; 61: 115–25.
[40]. Fu Y, Yang S, Jeong SH, Kimura S, Park K. Orally fast disintegrating tablets: Developments, technologies, taste-masking and clinical studies. Critical reviews in therapeutic drug carrier systems. 2004; 21(6):433-76.
[41]. Bhise K, Shaikh, S, and Bora D, "Taste Mask, Design and Evaluation of an Oral Formulation Using Ion Exchange Resin as Drug Carrier," AAPS Pharma Science Tech. June 2008; 9(2):557-62.
[42]. Hisakadzu S, Yunxia B. Preparation, evaluation and optimization of rapidly disintegrating tablets. Powder Technol. 2002; 122:188-98.
[43]. Bhasin RK, Bhasin N, Ghosh P. Advances in formulation of orally disintegrating dosage forms: A Review Article. Indo-Global Journal Pharma Science. 2011; 1(4):328-53.
[44]. Manivannan R. Oral disintegrating tablets: A future compaction. International Journal of Pharma Research. 2009; 1(10):1-10.
[45]. Agrawal V. A., Rajurkar R. M. "Fast disintegrating tablet as a new drug delivery system: A review". *International Research Journal Pharmacophore.* 2011; 2(1): 1-8.
[46]. Divate S., Kunchu K. "Fast disintegrating tablets-an emerging trend". International *Journal of Pharmaceutical Sciences Review and Research*. 2011; 6(2): 18-22.
[47]. Raichur V., Khanum A., Pandit V., Patel M., Rahman A., "Formulation Development of taste masking orally dissolving tablets of Cefpodoxime peometi using ion-exchange resins". *Indo-American J. of Pharm. Res.* 2014; 4(1): 151-165.
[48]. Gupta M. M., Gupta, N., Chauhan B. S., Pandey, S., "Fast Disintegrating Combination Tablet of Taste Masked Levocetrizine Dihydrochloride and Montelukast Sodium: Formulation Design, Development, and Characterization". *Hindawi Journal of Pharmaceutics,* 2014; 2(1): 1-15.
[49]. Pranavi P., Md. Gulsan, Gupta M. E., Rao R. N., "Formulation and evalution of immediate release Irbesartan pellets and tablets". *Indo-American J. of Pharm. Res.* 2014; 3: 1617-1624.
[50]. Metkavi V. B., Kulkarni L. V., Patil P. S., Jadav P. A., Jadav P. M., Yadav P. S., "Formulation and evalution of fast dissolving tablets of Carbamazepine using Solid dispersion". *Int. J. of Pharmacy Res. & Sci.* 2014; 2(1): 47-59.