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FORMULATION EVALUATION AND DEVELOPMENT OF FAST DISSOLVING TABLETS CONTAINING SOLID DISPERSION OF INDOMETHACIN

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Abstract:

The effectiveness of drug is depending upon the power of the dosage form to deliver the medicament to its site of action at a rate and amount sufficient to elicit the required pharmacological response. This property of dosage form is cited as physiologic availability, biologic availability or just bioavailability. Thus the term bioavailability is defined because the rate and extent of unchanged drug from its dosage forms.[1] The In-vivo performance of orally administered drugs depends upon their solubility and tissue permeability characteristics. BCS may be a scientific framework for classifying drug substances in line with their aqueous solubility and permeability. BCS guidelines are provided by U.S. Food and Drug Administration (USFDA), world Health Organization (WHO), European Medicines Agencies (EMEA). According to BCS classification, drug substances are grouped into four major classes

KEYWORDS- Solid Dispersion, Fast Dissolving,

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1. INTRODUCTION:

1.1 Solid Dispersion:

The concept of solid dispersion was proposed by Sekiguchi and Obi within the early 1960's, who investigated the generation and dissolution performance of eutectic, melts of a sulfonamide drug and water-soluble carrier. Solid dispersion represents a useful pharmaceutical method for increasing the dissolution, absorption and therapeutic efficacy of the drug within the dosage forms. The model of solid dispersion refers to a group of solid products containing of a minimum of two dissimilar components, generally a hydrophilic matrix and a hydrophobic drug.

1.2. Fast Dissolving Tablet:

1.2.1. Definition

US Food and Drug Administration (USFDA) defined fast dissolving tablet as "A solid dosage forms encompassing active ingredient or medical ingredients which disintegrates fast within a substance of seconds when placed upon the tongue." The disintegration time for fast dissolving tablets ranges from few seconds to a few minutes. Also, United state Pharmacopeia approved this dosage form as orally disintegrating tablet. European pharmacopeia defines an identical term, or dispersible tablets, that disperses rapidly within 3 minutes in mouth before swallowing. Over a decade, the demand for development of fast dissolving tablets has tremendously increased because it has impact on the patient's compliance. Fast dissolving tablets are beneficial for various groups of populations particularly who have difficulty in swallowing. Fast dissolving tablet also are appreciated by pediatric, geriatric patients, institutional patients together with mentally disabled patients who enable to require self-medication, and patients who tormented by nausea, vomiting and sickness complications. Fast dissolving tablets also are called as orodispersible tablets, orally disintegrating tablets, rapid dissolving tablets, quick disintegrating tablets, rapimelt tablets, fast disintegrating tablets. This dosage forms allow high patients compliance, high drug loading, have an honest mouth feeling and tastes, leaving minimal residue within the mouth after oral administration. Fast dissolving tablets enhances bioavailability of poorly water-soluble drugs. This dosage forms offers combined advantages of dry and liquid dosage formulations.

2. NEED OF PRESENT INVESTIGATION

Indomethacin belongs to a category of non-steroidal anti- inflammatory drugs. it's act by inhibiting isoforms of cyclooxygenase 1 and a pair of. Indomethacin employed in the treatment of moderate to severe autoimmune disorder including Marie-Strumpell disease, osteoarthritis, tendinitis, bursitis and acute urarthritis etc. Indomethacin is practically insoluble in aqueous medium and highly permeable belong to BCS class II. Indomethacin shows very low and variable oral bioavailability because of poor dissolution in gastrointestinal fluid. This unwanted property of Indomethacin gives irritating side effects in alimentary canal thanks to prolonged contact time with the mucosal layer of channel. Solid dispersion methods are accustomed overcome this problem. Solid dispersion is usually used technique to enhance dissolution and bioavailability of poorly soluble drugs. the rise in dissolution rate for solid dispersion are often attributed to number of things like particle porosity, particle size, wetting etc. Reduced particle size or reduced agglomeration, increased solubility or dissolution rate of poorly soluble drugs, transferring drug from crystalline form to amorphous form, soluble complex formation in microenvironment, saturation of drug in microenvironment, Solubalisation of poorly soluble drug in presence of surfactant are some mechanisms of solid dispersion. From the past decades, there has been enhanced demand for more patients' compliance dosage forms. Since the event cost of any new chemical drug is extremely high so for that reasons research and development department of the many pharmaceutical companies specializing in the event of latest drug delivery system for existing active ingredients. Novel drug delivery systems aims for designing and development of dosage forms, convenient to made and administered, with reduced side effects, offering rapid release and enhanced bioavailability so on achieve better patient compliance. In recent years, innovative drug delivery systems, like 'Fast Dissolving Tablets' are developed and attracted the interest of the many researchers. Fast dissolving tablets are ideal for several patients including elderly patients, children's, psychiatrics and for people who have difficulty in swallowing like stroke victims, and bedridden patients. Also fast dissolving tablet provide good mouth feel which helps to alter the perception of medication as bitter pill especially in children's. The basic concept utilized in development of fast dissolving tablet is to use various superdisintegrants like croscarmellose sodium, crospovidone etc. which give instantaneous disintegration of tablet after putting on tongue thereby releasing the active medicament in saliva. The saliva containing the dispersed or dissolved is then swallowed and also the drug may absorb in normal way. The bioavailability of poorly water-soluble drugs is also increased

because of absorption of medicine in rima oris and also thanks to pregastric absorption of medicine from mouth, pharynx and Oesophagus as saliva passes down in the stomach. The bioavailability of poorly water-soluble drugs could also be enhanced because of amount of drug that is subject to first pass metabolism is reduced as compared to traditional tablets. Therefore, in present work an endeavor was made to formulate fast dissolving tablets of Indomethacin using super disintegrants and using solid dispersion technique to reinforce dissolution rate and solubility of poorly water-soluble drug and provides enhanced patient compliance.

2.1 OBJECTIVES

In the present research work, fast dissolving tablets of Indomethacin are prepared by using solid dispersion technique and various superdisintegrants like crospovidone, croscarmellose sodium are used with direct compression method.

- To prepare solid dispersion of Indomethacin using PVP –K 30 as a carrier
- To evaluate prepared solid dispersion by drug content uniformity, % practical yield, Solubility study, in vitro dissolution study, FT-IR studies etc.
- To study the pre-compression parameters like bulk density, tapped density, Carr's index, Hausner's ratio, angle of repose etc.
- To formulate fast dissolving tablets containing solid dispersion of Indomethacin using superdisintegrants in different proportions by direct compression method.
- To formulate conventional tablets of Indomethacin without superdisintegrants and solid dipersion product by direct compression method.
- To evaluate prepared fast dissolving tablets containing solid dispersion by different post-compression parameters like hardness, friability, uniformity of thickness, weight variation, In- vitro disintegration time, drug content uniformity, In-vitro dissolution study ,FT-IR study , DSC studies etc.
- To evaluate prepared conventional tablets by different post- compression parameters
- To carry out comparative study of In-vitro dissolution of prepared fast dissolving tablets containing solid dispersion of Indomethacin with prepared conventional tablet of Indomethacin.

3. MATERIALS:

Table .No.1: List of ingredient

Sr. No.	Name of the ingredient
1	Indomethacin
2	PVP K-30
3	Crospovidone
4	Croscarmellose
5	Microcrystelline
6	Lactose
7	Magnesium stearate
8	Sodium saccharine
9	Talc

4. EXPERIMENTAL WORK:

4.1 Selection of Drug and Excipients:

In the present work, poorly water soluble non-steroidal anti-inflammatory drugs viz Indomethacin is selected. Indomethacin is used in treatment of rheumatoid arthritis, acute gouty arthritis, spondylitis, osteoarthritis.

4.2 Preformulation Study Of Drug:

4.2.1 Melting point determination:

Melting point of pure Indomethacin was determined by open capillary method. The capillary tube was closed at one end by fusion and was filled with Indomethacin and placed in Thiele"s melting point apparatus and the temperature at which the drug melted by was noted.

4.2.2 Determination of max of Indomethacin in phosphate buffer 6.8

100 mg of pure drug transferred into 100 ml of phosphate buffer 6.8 in a volumetric flask. Withdrawn 10 ml sample from this solution and diluted to 100ml it make 100mcg/ml(stock solution) then concentration make by withdrawing 1 ml from the stock solution and diluted to 100 ml it makes solution of concentration 10 g/ml. Finally, the standard solution (10µg/ml) of Indomethacin in phosphate buffer pH 6.8 was scanned between 200-400 nm on UV- visible spectrophotometer to record the wavelength of maximum absorption (λ max).

4.2.3 Determination of calibration curve of Indomethacin in phosphate buffer 6.8:

100 mg of pure drug transferred into 100 ml of

phosphate buffer 6.8 in a volumetric flask. Withdrawn 10 ml sample from this solution and diluted to 100ml it make 100 mcg/ml(stock solution) then concentration make by withdrawing 0.5,1,1.5, 2 , 2.5, 3 ,3.5,4,4.5,5ml from the stock solution and diluted to 100 ml it makes solution of concentration 5 g/ml,10 g/ml,15 g/ml, 20 g/ml, 25 g/ml, 30 g/ml, 35 g/ml, 40 g/ml, 45 g/ml, 50 g/ml Absorbance was measured for each solution at max 319 nm using UV Visible Spectrophotometer, graph was plotted for absorbance verses concentration of Indomethacin.

4.2.4 Differential scanning calorimetry (DSC)

DSC was performed in order to assess the thermotropic properties and thermal behavior of the drug (Indomethacin). Differential scanning calorimetry thermogram of the pure drug was recorded on a thermal analyzer. The samples were heated from 25 to 500 °C at a heating rate of 10 °C/min in an inert nitrogen atmosphere.

4.2.5 Fourier Transform Infra-Red (FTIR) Spectroscopy:

Infrared spectrum of Indomethacin was determined on Fourier Transform Infrared spectrophotometer Small quantity of sample was taken and directly put on IR platform. Then the spectra were scanned over wavelength region of 4000 to 400 cm-1 at resolution of 4 cm1.

4.3 Method of Preparation of Solid Dispersion Systems

a. Solvent Evaporation Method

An accurate amount of Indomethacin and carrier was dissolved in minimum quantity of ethanol with continues stirring .The solvent was removed at 45oc - 400c until the solid dispersion dry. The dried mass was pulverized, passes through 100 mesh sieve and was stored in desiccators until used for further studies.

b. Physical mixture:

Physical mixtures were prepared by mixing Indomethacin with PVP K -30 fo three minutes in a mortar until a homogeneous mixture was obtained. The resulting mixture was sieved through sieve no. 100 and then stored in desiccators at room temperature until use.

4.3.1 Evaluation of Solid Dispersion:

I. Physical Appearance:

All the batches of Indomethacin solid dispersion were evaluated for colour and appearance

II. Drug content uniformity:

The solid dispersion equivalent to 100 mg of drug were taken and dissolved minimum amount of ethanol and then diluted up to in100 ml of phosphate buffer 6.8 .The solutions were filtered and were further diluted such that the absorbance falls within the range of standard curve. The absorbance of solutions was determined at 319 nm by UV-visible spectrophotometer. The actual drug content was calculated using the following equation

Drug content = Actual Indomethacin content in solid dispersion/ Theoretical amount of Indomethacin in solid dispersion* 100

III. % Practical Yield

Percentage practical yield is calculated to know about percent yield or efficiency of any method, thus its help in selection of appropriate method of production. Solid dispersions to determine by practical yield from the following equation.

Practical Yield (%) =
Practical Mass (Solid dispersion)/Theoretical Mass (Drug + carrier) ×100

IV. Solubility study

An excess amount of Indomethacin in distilled water and solid dispersions of Indomethacin using carrier in 20 ml of phosphate buffer PH 6.8 was placed in conical flask. All conical flask remained closed with stopper and enclosed with cellophane membrane to Prevent solvent loss. All flasks were placed in mechanical shaker for 72 hours at room temperature. After that all contains in flasks was filtered through 0.45 mm. The filtrate was diluted suitably and measured by spectroscopically. All solubility measurement was performed in triplicate.

V. *In -vitro* dissolution studies

Dissolution studies were performed in phosphate buffer (pH 6.8, 900 ml) at 37 ± 0.5 °C, using USP type II with a paddle rotating at 50 rpm. The solid dispersions equivalent to 25 mg of Indomethacin was taken in a muslin cloth and tied to the rotating paddle kept in the basket of dissolution apparatus. At fixed time intervals, samples (5 ml) were withdrawn and equal amount of fresh dissolution medium was added. Withdrawn samples were filtered through 0.45 µm membrane filter, and spectrophotometrically assayed for drug content at 319 nm wavelengths using a UV-VIS spectrophotometer.

VI. Differential scanning calorimetry (DSC)

DSC was performed in order to assess the thermotropic properties and thermal behavior of the drug (Indomethacin) and carrier. Differential scanning calorimetry thermogram of the solid dispersion of Indomethacin was recorded on a

thermal analyzer. The samples were heated from 25 to 500 °C at a heating rate of 10 °C/min in an inert nitrogen atmosphere.

VII. Fourier Transform Infrared spectroscopy

IR study was carried out to check compatibility between drug and excipients. Infrared spectrum of Indomethacin solid dispersion was determined on Fourier Transform Infrared spectrophotometer. The baseline correction was done using dried potassium bromide. Then small quantity of sample was taken and directly put on IR platform.

4.4 Method of Preparation of Fast Dissolving Tablets

In this work, direct compression method with the aid of superdisintegrants was attempted for the formulation development of fast dissolving tablets containing solid dispersion of Indomethacin. The promising solid dispersion formulations were further formulated as fast dissolving tablets using suitable superdisintegrants. Dose of 25 mg is selected for the present study.

Development of fast dissolving tablets formulation in the present study was based on the type and concentration of superdisintegrants. Two different superdisintegrants were used in different concentration so as to get tablet with good physical properties. The formulation design of fast dissolving tablets of Indomethacin is shown in table no.2 and 3

Table No.2: Formulation of fast dissolving tablets containing Indomethacin solid dispersion formulation (PM3

Ingredients (mg)	TP1	TP2	TP3	TP4	TP5
Amount of solid dispersion equivalent to 25 mg	200	200	200	200	200
Microcrystelline cellulose	80	80	80	80	80
Crosprovidone			16	20	10
Croscarmellose sodium	16	20			10
Sodium saccharine	3	3	3	3	3
Magnesium stearate	3	3	3	3	3
Talc	3	3	3	3	3
Lactose	95	91	95	91	91
Total	400	400	400	400	400

Where,

TP1and TP2 –Tablets prepared by using solid dispersion product prepared by physical mixture method. [Containing 4% and 5% croscarmellose sodium respectively]

TP3and TP4 –Tablets prepared by using solid dispersion product prepared by physical mixture method. [Containing 4% and 5% crospovidone respectively]

TP5 –Tablets prepared by using solid dispersion product prepared by physical mixture method. [Containing 2.5 % croscarmellose sodium+2.5 % crospovidone]

Table No.3: Formulation of fast dissolving tablets containing Indomethacin solid dispersion formulation (SE3)

Ingredients (mg)	TS1	TS2	TS3	TS4	TS5
Amount of solid dispersion equivalent to 25 mg	184	184	184	184	184
Microcrystelline cellulose	80	80	80	80	80
Crosprovidone			16	20	10
Croscarmellose sodium	16	20			10
Sodium saccharine	3	3	3	3	3
Magnesium stearate	3	3	3	3	3
Talc	3	3	3	3	3
Lactose	111	107	111	107	107
Total	400	400	400	400	400

Where,
TS1and TS2 –Tablets prepared by using solid dispersion product prepared by solvent evaporation method. [Containing 4% and 5% croscarmellose sodium respectively]
TS3and TS4 –Tablets prepared by using solid dispersion product prepared by solvent evaporation method. [Containing 4% and 5% crospovidone respectively]
TS5 –Tablets prepared by using solid dispersion product prepared by solvent evaporation method. [Containing 2.5 % croscarmellose sodium+2.5 % crospovidone]

Table No.4: Formulation of conventional tablets of Indomethacin by direct compression method

Ingredients (mg)	Qty
Indomethacin	25
Microcrystelline cellulose	80
Sodium saccharine	3
Magnesium stearate	3
Talc	3
Lactose	q.s.

4.4.1 Preparation of fast dissolving tablets of Indomethacin by direct compression method:
Fast dissolving tablets of Indomethacin were prepared by direct compression method according to the formula given in table no.8 and 9. All the components were delivered through 40 mesh sieve separately. The solid dispersion containing 25 mg Indomethacin and diluents was mixed by small portion of both each time and blending I to get a uniform mixture then other ingredients were mixed in geometrical order. Prepared blend was compressed (10mm Punch) using multi station tablet press machine (Shakti, Ahemadabad, India).

4.4.2 Preparation of conventional tablets of Indomethacin by direct compression method:
Conventional tablets of Indomethacin were prepared by direct compression method according to the formula given in table.no.10. All the ingredients were passed through 40 mesh sieve separately. Prepared blend was compressed (10mm Punch) using tablet punching Machine.

4.5 Evaluation of Fast Dissolving Tablets:

I. Pre-compression parameters:

Determination of angle of repose, Carr‟s index and Hausner‟s ratio were accustomed characterize flow properties of the solid dispersion systems. The flow ability of a powder is also a critical importance within the assembly of pharmaceutical dosage forms so on urge a regular feed likewise as reproducible filling of tablet dies, otherwise, high dose variation will occur.

1) Angle of repose:

Angle of repose has been used as unintended methods of quantifying powder flow capability. Angle of repose is defined because the utmost angle possible between the surface of pile of the powder and surface the frictional force in an exceedingly very loose powder or granules is decided by angle of repose. Angle of repose for blend of each formulation determined by fixed funnel method. The angle of repose resolves by substituting the values of the underside radius „r ‟and height of the pile "h" within the formula given below,

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

h =is the height in cm and

r =is the radius.

Table No.5: Relation between angle of repose (θ) and flow properties

Angle of repose (degrees)	Flow
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

2) Bulk density:

Bulk density was determined by pouring pre-sieved drug and excipients blend into a graduated cylinder and measuring the volume and weight "as it is". It is expressed in g/ml and is given by

Db = M / V0

Where,

M is the mass of powder

V0 is the Bulk volume of the powder

3) Tapped density:

Bulk density make up my mind by pouring pre-sieved drug and excipients blend into a graduate and measuring the degree and weight "as it is". it's expressed in g/ml and is given by

Dt = M / Vt

Where,

M is the mass of powder

Vt is the tapped volume of the powder.

4) Carr's Index (%Compressibility):

The compressibility index and Hausner ratio are measures of the property of powder to be compressed. The packing ability of drug was evaluated from change in volume, which is thanks to rearrangement of packing occurring during tapping. it absolutely was indicated as Carr‟s compressibility index was calculated as follows.

Carr's index% = [Tapped density - Bulk density/Tapped density] X 100

Table No 6: Grading of powders for their flow properties according to Carr's index

Consolidation index (Carr's%)	Flow
5-15	Excellent
12-16	Good
18-21	Fair to passable
23-35	Poor
33-38	Very poor
40	Very very poor

5) Hausner Ratio:

Measurement of frictional resistance of the drug. He showed that the powder with low inter particle friction had ratio of roughly 1.2, whereas more cohesive less free flowing powder have Hausner‟s ratio greater than 1.6 . Hausner‟s ratio but 1.25 indicate good flow properties. it had been determined by the ratio of tapped density and bulk density

Hausne r Ratio = Tapped density / Bulk density

II. Post compression Parameters:

Prepared tablets were subjected to evaluation of assorted properties including tablet hardness, friability, uniformity of thickness, In vitro disintegration time, In vitro dissolution test etc.

1) Hardness:

Hardness indicates the ability of a tablet to face to mechanical shocks while handling. The hardness of the tablets determined using Monsanto hardness tester. it's expressed in Kg/cm2. Three tablets were randomly picked and mean hardness of the tablets formulation was determined.

2) Friability:

Tablet hardness is not an absolute indicator of strength, since some formulations compressed into very hard tablet tend to cap on attrition losing their crown potions. Therefore another measure of tablet

strengths, its friability is often measured. The friability of tablets was determined using Roche friabilator. It is expressed in percentage (%). Twenty tablets were initially weighed and transferred into friabilator. The friabilator was operated at 25rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again .The % friability was then calculated by Percentage friability of tablets less than 1% is considered acceptable.

3) Weight Variation Test:

The weight of tablets is measured to confirm that a tablet contain the correct amount of drug. Twenty tablets were selected indiscriminately and therefore the average weight was firm. USP official limits of percentage deviation of tablet are presented within the table no. 13 Average weight of tablet Percent deviation

130 mg or less 10

More than 130 mg or less than 324 mg

7.5

More than 324 mg or more 5 100

Initial weight of the tablets

Initial weight of the tablets – Final weight ofthe tablets

% Friability X

In all the formulations the tablet weight was 400 mg, hence 5% maximum difference allowed.

4) Uniformity of Thickness:

The thickness of the tablets determined employing a callipers. Three tablets from each variety of formulation were used and average values were calculated. it's expressed in mm.

5) Uniformity of Drug Content:-

Five tablets of every kind of formulation were weighed and crushed in mortar and powder love 25 mg of drug transferred in conical flask containing 25 ml phosphate buffer 6.8. Its concentration 1000mcg/ml.10 ml from this stock solution was taken and diluted to 100 ml phosphate buffer 6.8.; it makes 100 g/ml. Then 25 g/ml solution prepared by taking 2.5 ml from this stock solution and diluted up to 10 ml. Absorbance measured at 319 nm.

6) Wetting Time:

A piece of paper folded twice containing was placed in an exceedingly small Petri dish (ID =6.5 cm) containing 10 ml of phosphate buffer 6.8, a tablet was placed on the paper and also the time required for complete wetting was measured as wetting time. The study was performed in triplicate.

7) In -vitro disintegration time:

Generally accepted maxima is that for a drug to be readily available to the body, it must be in solution form. for many of the tablets the primary important step toward solution is breakdown of the tablet into smaller particles, a process called disintegration. In vitro disintegration time is measure using is integration test apparatus as per I.P. specifications. I.P. specifications: Place one tablet in each of the 6 tubes of the basket. Add a disc to every tube and run the apparatus using phosphate buffer 6.8 maintained at 370±2°C because the immersion liquid. The assembly should be raised and lowered between 30 cycles per minute within the pH 6.8 maintained at 370±2°C. The time in seconds taken for complete disintegration of tablet with no palpable mass remaining within the apparatus was measured and recorded. The assembly was off from liquid. The tablets pass the test if all of them have disintegrated. If 1 or 2 tablets fail to disintegrate repeat the test for 12 additional tablets; not but 16 of the overall of 18 tablets tested disintegrate, finally observe the disintegration time of the tablets.

8) *In-vitro* dissolution study:

he release rate of Indomethacin from fast dissolving tablets was resolute using United State Pharmacopoeia (USP) dissolution testing apparatus II (paddle method). The dissolution test was performed using 900 ml of phosphate buffer 6.8 dissolution medium, at 37±0.5°C and 50 rpm. Sample volume of 5 ml was withdrawn at every 1 minute measure and filtered. the amount withdrawn was replaced by fresh volume of dissolution medium to take care of constant volume of medium. The filtered samples were analyzed spectrophotometrically at 319 nm using phosphate buffer 6.8 as a blank. Drug content in dissolution sample decided by calibration curve. The study was dole out in triplicate.

9) Differential scanning calorimetry (DSC) of fast dissolving tablets:

DSC was performed so as to assess the thermotropic properties and thermal behavior of oral fast dissolving tablets prepared. Differential scanning calorimetry thermograms of optimized tablet formulation were recorded on a thermal analyzer. The samples were heated from 25 to 500 °C at a heating rate of 10 °C/min in an inert nitrogen atmosphere.

10) Fourier Transform Infra-Red (FTIR) Spectroscopy of fast dissolving tablets:

IR spectroscopy is one amongst the qualitative analytical techniques, which offers the chance of detecting chemical interaction. Infrared spectra of optimized formulations were determined on Fourier

Transform Infrared Spectrophotometer using KBr dispersion method. the bottom-line correction was done using dried restrainer. Then the spectrum of physical mixture of drug and restrainer was recorded.

4.6 Comparative study of optimized formulation of fast dissolving tablets with prepared conventional tablets of Indomethacin

The release rate of conventional tablets of Indomethacin and optimized formulations of fast dissolving tablets were determined using United State Pharmacopoeia (USP) dissolution testing apparatus II (paddle method). The dissolution test was performed using 900 ml of phosphate buffer 6.8 dissolution medium, at 37±0.5°C and 50 rpm. Sample volume of 5 ml was withdrawn at every 1 minute amount and filtered. the amount withdrawn was replaced by fresh volume of dissolution medium to keep up constant volume of medium. The filtered samples were analyzed spectrophotometrically at 319 nm using phosphate buffer 6.8 as a blank. Drug content in dissolution sample determined by calibration curve. The study was administrated in triplicate. the discharge rate of Indomethacin from conventional tablets was compared with release rate of Indomethacin from optimized formulations of fast dissolving tablets

5. RESULTS AND DISCUSSION:

5.1 Preformulation Study of Drug:

5.1.1 Melting Point-

The melting point of Indomethacin was found to be 1610c which complies with range that given in the literature i.e. 158-1620c.

5.1.2 Determination of λ max of the Indomethacin-

The standard solution of Indomethacin shows maximum absorbance at 319 nm wavelength in spectroscopy.

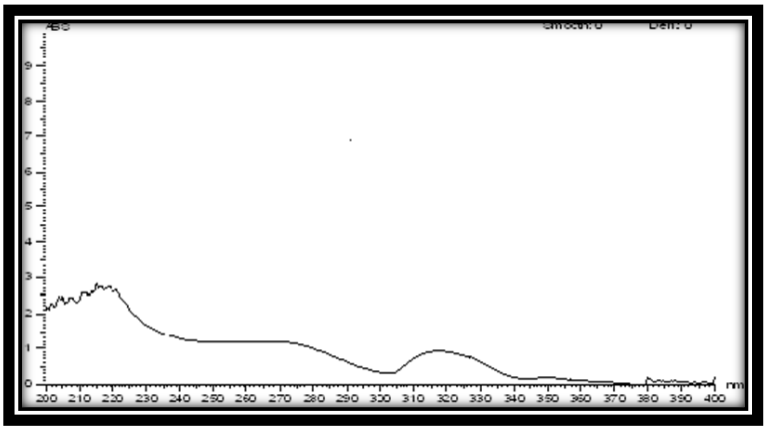

Fig. No.1: UV spectrum of Indomethacin

5.1.3 Preparation of standard calibration curve of Indomethacin

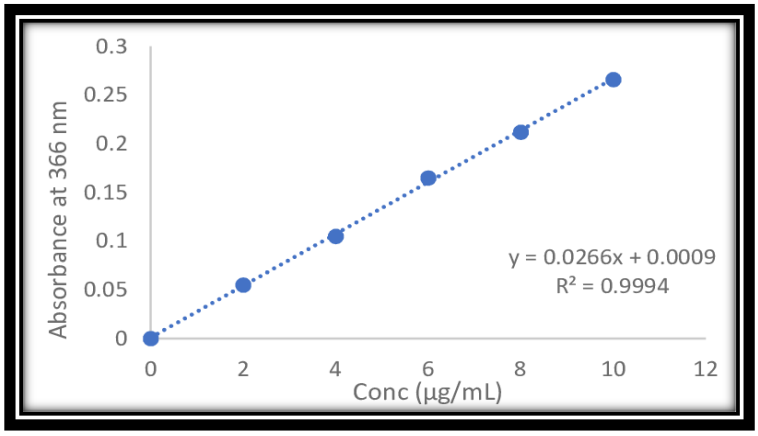

Fig. No.2: Standard calibration curve of Indomethacin in pH 6.8 phosphate buffer at 319nm

Table. No.7: Observations for standard calibration curve of Indomethacin in pH6.8 phosphate buffer at 319 nm66

Sr. no	Concentration	Absorbance
1	0	0
2	5	0.0084
3	10	0.1859
4	15	0.2637
5	20	0.3545
6	25	0.4573
7	30	0.5574
8	35	0.6325
9	40	0.7184
10	45	0.8147
11	50	0.9158

Calibration Curve

Table. No.8: Standard curve statistics

Sr. No	Parameters	Observations
1	Absorbance maximum	319
2	Slope	0.0018
3	Intercept	-0.023
4	Coefficient of correlation	0.994

5.1.4 Differential scanning colorimetry (DSC):

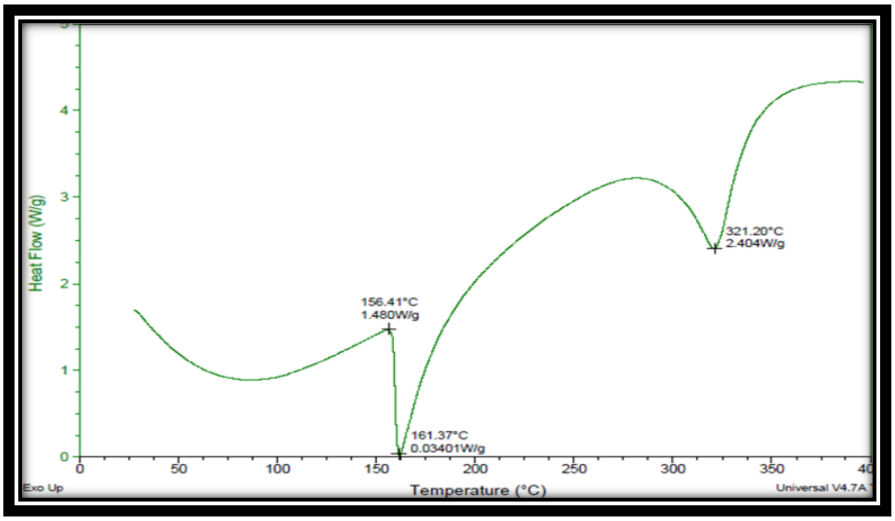

Fig. No 3: DSC of Pure Indomethacin

5.1.5 Fourier Transform Infra-Red (FTIR) Spectroscopy:

An IR spectrum of Indomethacin is presented in figure no 18. Observed peaks are shown in table no.16 these peaks are similar to reported peaks of Indomethacin.

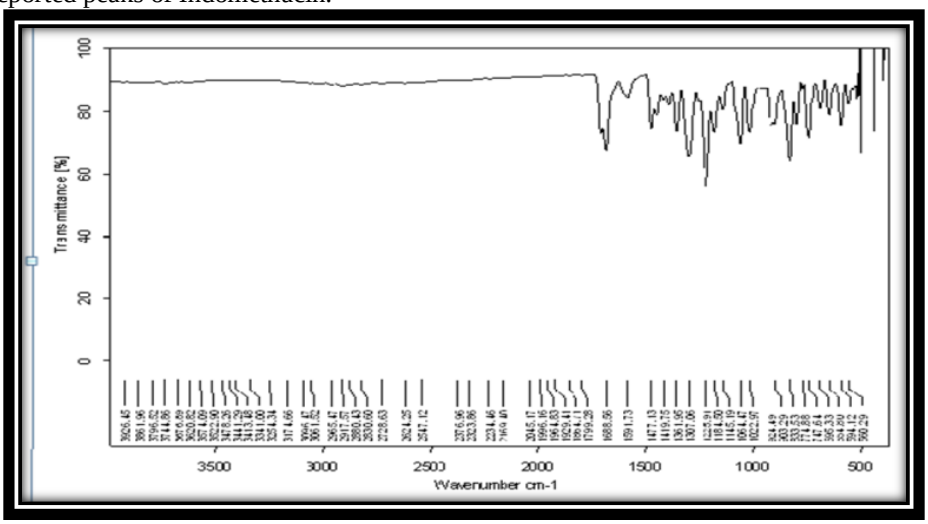

Fig. No.4: FTIR Spectrum of Pure Indomethacin

Table No.9: Observed peaks of FTIR spectra of Indomethacin

Functional group	Observed wave numbe r (cm^{-1})
C=O in ketone	1688.56
OH in –COOH group	1477.13
C=O in COOH group	1307.06
C=C in aromatic alkene	1145.19

Table No.10: Physical parameters of Indomethacin solid dispersion.

Formulation Code	Physical Appearance	
	Colour	Appearance
PM1	White	Fine powder
PM2	White	Fine powder
PM3	White	Fine powder
SE1	Light yellow	Fine powder
SE2	Light yellow	Fine powder
SE3	Light yellow	Fine powder

A) Drug content uniformity of Indomethacin solid dispersion:

Table No.11: Drug content, Percent practical yield, solubility study of Indomethacin solid dispersion:

Formulations	Drug content Uniformity (%) SD	% Practical Yield	Solubility in PBS 6.8 (g/ml) SD
ID	-	-	0.5203 0.008
PM1	79.56 0.13	90	1.081 0.08
PM2	88.39 0.13	100	1.059 0.07
PM3	98.65 0.17	100	1.464 0.01
SE1	97.43 0.17	54	1.602 0.002
SE2	98.86 0.47	68	1.860 3.02
SE3	99.59 0.13	92	3.339 0.05

B) % practical yield of Indomethacin solid dispersion:
The % practical yield of all six formulations are shown in table no.18 .The % practical yield of all six formulations was found to be in the range of 54% to 92%. The maximum % practical yield was found to be 92 % in SE3.

C) Solubility study of Indomethacin solid dispersion:
Solubility study of solid dispersion of Indomethacin prepared by physical mixture method and solvent evaporation method the solubility studies of solid dispersions were carried out in PBS 6.8.The solubility of Indomethacin was very less as compared to solid dispersions of Indomethacin. The solubility studies of all six formulations are shown in table no.18. The maximum solubility was found in formulation SE3 (1:5) which was prepared by solvent evaporation method. As the proportions of PVP K- 30 increased, the solubility of Indomethacin also increases .All the solid dispersions show higher solubility as compared to pure Indomethacin.

D) Differential scanning calorimetry (DSC) studies of Indomethacin solid dispersion:

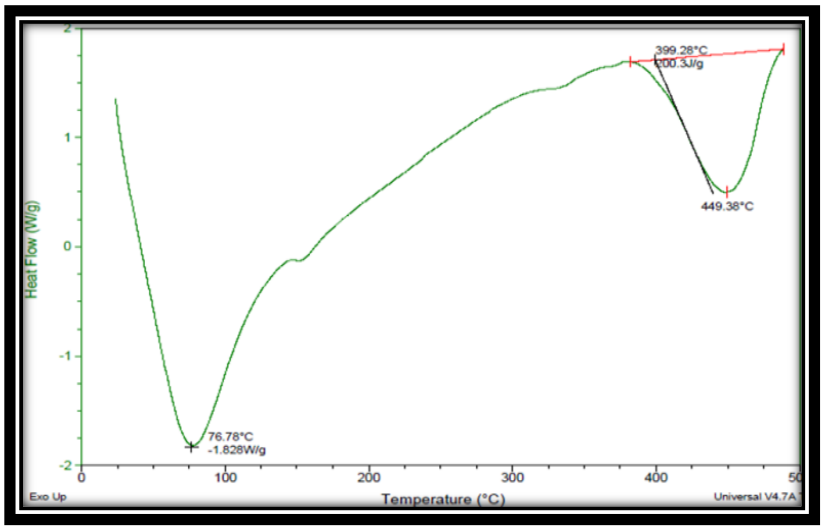

Fig. No.5: DSC of Indomethacin solid dispersion formulation (PM3)

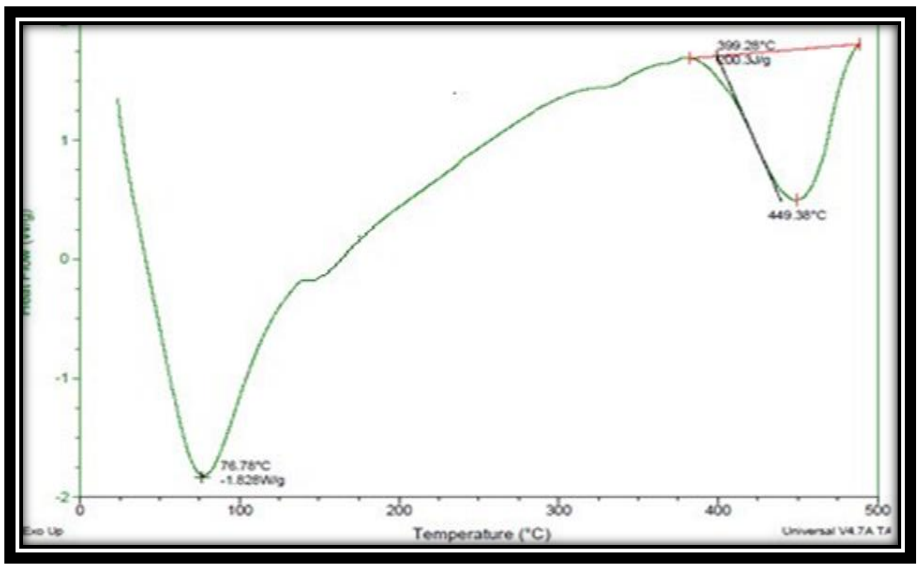

Fig. No.6: DSC of Indomethacin solid dispersion formulation (SE3)

E) Fourier Transform Infrared spectroscopy studies of Indomethacin solid dispersion:

Table No.12: Observed peaks of FTIR spectra of Indomethacin solid dispersion Formulations (PM3)

Functional group	Observed wave numbe r (cm^{-1})
C=O in ketone	1684.02
OH in –COOH group	1449.40
C=O in COOH group	1362.36
C=C in aromatic alkene	1145.77

Table No.13: Observed peaks of FTIR spectra of Indomethacin solid dispersion formulations (SE3)

Functional group	Observed wave numbe r (cm^{-1})
C=O in ketone	1591.73
OH in –COOH group	1419.75
C=O in COOH group	1361.95
C=C in aromatic alkene	1134.50

5.2 Evaluation of Solid Dispersion Incorporated Indomethacin Fast Dissolving Tablet and Conventional Tablet:

I. Results of Pre-compression Parameters:

Table No.14: Results of Pre-Compression Parameters:

Formulation code	Angle of repose (degrees)	Bulk Density g/cc	Tapped Density g/cc	Hausner's Ratio	Carr's Index %
CT	22.45 0.11	0.421 0.15	0.478 0.23	1.09 0.01	12.35 1.35
TP1	16.18 0.66	0.450+0.13	0.492 0.15	1.09 0.02	8.36 2.13
TP2	20.00 0.90	0.418+0.19	0.502 0.15	1.10 0.005	9.53 0.45
TP3	22.90 0.24	0.466+0.10	0.455 0.08	1.15 0.08	9.68 1.99
TP4	20.47 0.90	0.547+0.14	0.503 0.05	1.14 0.02	12.99 2.17
TP5	21.56 0.91	0.739+0.29	0.665 0.14	1.09 0.02	8.48 2.32
TS1	17.98 0.69	0.466+0.24	0.444 0.11	1.19 0.02	9.73 2.38
TS2	19.02 0.30	0.478+0.34	0.545 0.12	1.09 0.02	8.91 1.69
TS3	21.29 0.57	0.581+0.21	0.637 0.13	1.12 0.01	10.83 1.4
TS4	20.67 0.35	0.814+0.49	0.532 0.11	1.12 0.03	11.33 2.5
TS5	21.80 0.39	0.525+0.30	0.502 0.13	1.08 0.03	8.18 2.61

All value are expressed as mean ± SD,

II. Result of Post -Compression Parameters:

Table No.15: Results of post-compression parameters for the tablets like hardness, friability, weight variation, and uniformity of thickness:

Formulation code	Hardness Kg/cm$_2$	Friability %	Weight Variation mg	Uniformity of thickness
CT	3.2 0.2	0.51	396 0.62	3.2 0.15
TP1	3.2 0.2	0.64	397 0.48	3.3 0.20
TP2	3.2 0.2	0.47	397 0.90	3.2 0.11
TP3	3.2 0.31	0.66	31396 0.90	3.1 0.17
TP4	3.1 0.11	0.40	395 0.55	3.2 0.1
TP5	2.9 0.23	0.52	396 0.7	3.2 0.15
TS1	3.1 0.05	0.68	397 1.06	3.2 0.11
TS2	3.1 0.11	0.54	397 1.22	3.4 0.41
TS3	3 0.2	0.32	396 0.85	3.1 0.15
TS4	3.0 0.23	0.41	396 0.80	3.2 0.11
TS5	3.0 0.30	0.32	395 0.99	3.2 0.15

All value is expressed as mean ± SD, n=3

Table No.16: Results of post-compression parameters for the tablets

Formulation code	Drug content Uniformity %	Wetting Time sec	In -vitro Disintegration time sec
CT	99.09 0.04	186 2	263 2.08
TP1	90.67 0.01	49 2.64	57 1.73
TP2	98.56 0.39	44 2	56 2
TP3	93.51 3.06	41 1	54 2
TP4	94.25 0.11	41 1	54 1
TP5	99.51 0.23	46 2	56 2.64
TS1	93.83 0.05	26 1.73	45 1.73
TS2	98.07 0.11	30 3.60	35 2.64
TS3	95.86 0.2	32 2	51 1.73
TS4	99.34 0.23	20 1	33 1.73
TS5	98.99 0.30	17 1	28 1

All value are expressed as mean ± SD, n=3

5.2.1 *In -vitro* disintegration time sec:

The results of In -vitro disintegration time were found to be in the range of 28 to 56 sec and tabulated in table no.22. The disintegration time of conventional tablet of Indomethacin was found to be 263 sec. The results of disintegration time indicated that fast dissolving tablets have shown much less disintegration time as compared to In –vitro disintegration time of conventional tablets.

5.2.2 *In- Vitro* dissolution studies:

Table No.17: Cumulative % drug release profile of TP1, TP2, TP3, TP4, TP5

Time (min)	Cumulative % drug release				
	TP1	**TP2**	**TP3**	**TP4**	**TP5**
0	**0**	**0**	**0**	**0**	**0**
1	43.99 1.05	62.98 0.16	59.77 0.6	64.95 0.14	64.74 0.38
2	46.93 0.61	68.27 0.18	68.85 0.9	67.79 0.16	70.94 0.33
3	70.94 0.33	59.37 0.83	70.12 0.14	73.98 0.12	74.85 0.32
4	49.53 0.10	71.09 0.18	72.86 0.37	78.97 0.14	84.75 0.28
5	59.11 0.17	83.78 0.15	74.22 0.12	86.50 0.14	87.67 0.26
6	62.19 0.11	85.03 0.17	79.02 0.19	95.03 0.15	89.79 0.17
7	72.42 0.25	87.38 0.14	84.14 0.14	97.76 0.18	92.77 0.26
8	83.63 0.25	92.78 0.18	90.95 0.19	99.41 0.18	95.43 0.21
9	84.74 0.36	96.77 2.79	98.70 0.34	-	99.63 0.14
10	89.74 0.10	98.52 0.17	99.37 0.14	-	-
11	96.99 0.13	-	-	-	-

All value are expressed as mean ± SD, n=3

Table No.18: Cumulative % drug release profile of TS1, TS2, TS3, TS4, TS5

Time (min)	Cumulative % drug release				
	TP1	TP2	TP3	TP4	TP5
0	0	0	0	0	0
1	9.81 0.18	62.98 0.16	59.77 0.6	64.95 0.14	64.74 0.38
2	46.93 0.61	68.27 0.18	68.85 0.9	67.79 0.16	70.94 0.33
3	70.94 0.33	59.37 0.83	70.12 0.14	73.98 0.12	74.85 0.32
4	49.53 0.10	71.09 0.18	72.86 0.37	78.97 0.14	84.75 0.28
5	59.11 0.17	83.78 0.15	74.22 0.12	86.50 0.14	87.67 0.26
6	62.19 0.11	85.03 0.17	79.02 0.19	95.03 0.15	89.79 0.17
7	72.42 0.25	87.38 0.14	84.14 0.14	97.76 0.18	92.77 0.26
8	83.63 0.25	92.78 0.18	90.95 0.19	99.41 0.18	95.43 0.21
9	84.74 0.36	96.77 2.79	98.70 0.34	-	99.63 0.14
10	89.74 0.10	98.52 0.17	99.37 0.14	-	-
11	96.99 0.13	-	-	-	-

5.2.3 Differential scanning colorimetry (DSC):

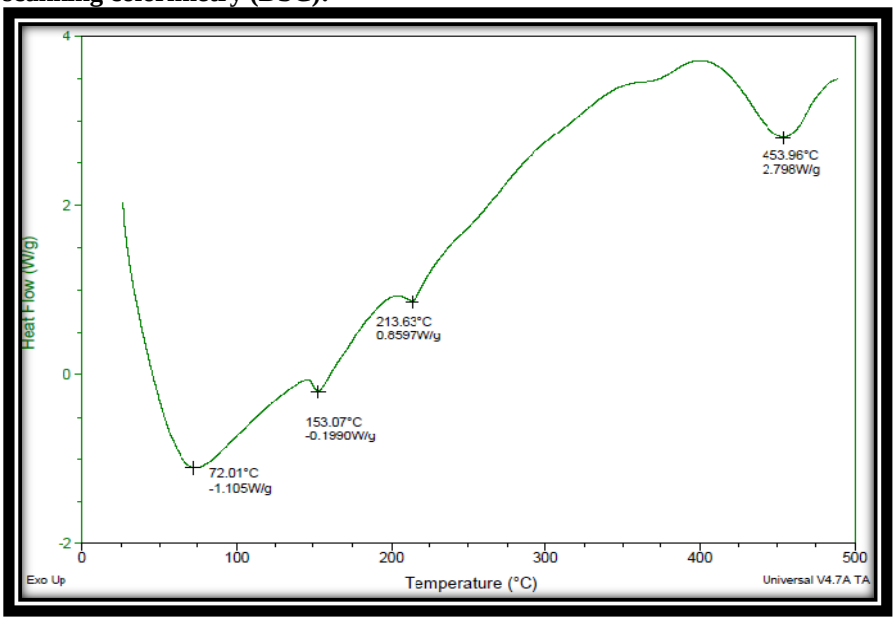

Fig. No.7: DSC of Optimized formulations of fast dissolving tablets TS4

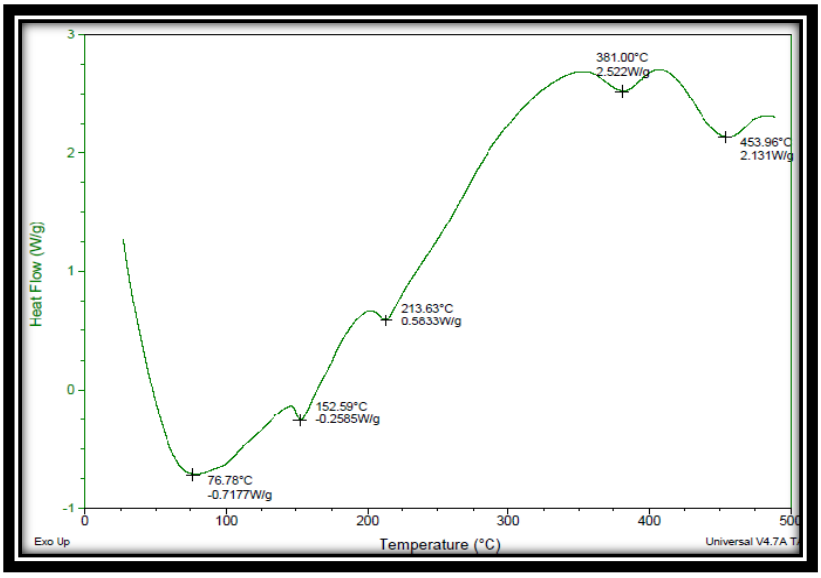

Fig. No .8: DSC of Optimized formulations of fast dissolving tablets TS5

5.2.4 Fourier Transform Infra-Red (FTIR) Spectroscopy

Table No.19: Observed peaks of FTIR spectra of optimized formulation of fast dissolving tablets containing solid dispersions of Indomethacin TS4

Functional group	wave numbe r (cm^{-1})
C=O in ketone	1684.02
OH in –COOH group	1449.40
C=O in COOH group	1364.36
C=C in aromatic alkene	145.77

Table No.20: Observed peaks of FTIR spectra of optimized formulation of fast dissolving tablets containing Table solid dispersions of Indomethacin TS5

Functional group Observed	wave numbe r (cm^{-1})
C=O in ketone	1645.29
OH in –COOH group	1461.06
C=O in COOH group	1338.15
C=C in aromatic alkene	1162.89

5.3 Comparative study of optimized formulation of fast dissolving tablets with prepared conventional tablets of Indomethacin

Table No.21: Cumulative % drug release profile of CT, TS4, and TS5

Time (min)	CT	TS4	TS5
0	**0**	**0**	**0**
1	9.72	65.82 0.18	67.30 0.18
2	10.22	70.98 0.16	75.00 0.11
3	10.45	74.54 0.18	88.24 0.18
4	10.95	84.21 0.20	95.03 0.21
5	11.43	86.62 0.18	97.78 0.18
6	11.69	93.04 0.09	99.94 0.14
7	12.16	96.19 0.10	-
8	12.58	-	-
9	13.48	-	-
10	14.52	-	-
11	15.36	-	-

6. SUMMARY AND CONCLUSION:

In present study was an attempt was made to develop fast dissolving tablets containing solid dispersion of NSAID by using PVP K30 as a carrier and crospovidone and croscarmellose sodium as a per disintegrants. From data obtained from formulation and evaluation of dissolving tablet, following conclusions were made:

The solid dispersions of Indomethacin were prepared by physical mixture and solvent evaporation method using PVP K 30 as a carrier in the ratio of 1:3, 1:5, and 1:7 weights respectively. The solubility and dissolution rate of Indomethacin from solid dispersion (SE3) were increased in presence of PVP K 30 as that of pure Indomethacin drug. Among the two methods, solvent evaporation method is better efficient than that of physical mixture method.PVP K 30 proved to be the good carrier for preparation of solid dispersion of poor water-soluble drug like Indomethacin.

All the observations of pre-compression parameters and post-compression parameters of fast dissolving tablets and conventional tablets were observed within the range. All observations of In vitro1 disintegration time of fast dissolving tablets less than 1 min which comply within standards. It can be concluded that formulation TS5 shows highest drug release than formulation TS4 because combination of two superdisintegrants gives synergistic effect on disintegration of tablet, as compared to individual use.

It can be concluded that formulation TS4 and TS5 shows highest drug release than conventional tablets formulation .TS5 shows very fast drug release, as compared to formulation TS4 and conventional tablet because, in formulation TS5, two superdisintegrants were used in same proportion [i.e.2.5 %+2.5 %]. These two superdisintegrants were shown combined synergistic effects on drug release, and hence giving fast disintegration.

From all above results, it can be concluded that, solvent evaporation method is very good method of solubility enhancement of drug. Croscarmellose sodium and crospovidone both superdisintegrants when used in combination gives synergistic effect on disintegration of tablet, as compared to their individual use.

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