Subscription Agency
Exploring and Distributing Knowledge Globally

Journal of Advancement in Pharmacology
Volume 2 Issue 1, 2022

Preparation and Evaluation of Etoricoxib Fast Dissolving Tablet by Employing Various Superdisintegrants

Nilam Shrestha*, Meenakshi Kukshal, Shivanand Patil, Ayush Acharya
Department of Pharmacy, Shree Dev Bhoomi Institute of Education, Science and Technology, Uttarakhand Technical University, Erandwane, Poundha, Premnagar, India.

Corresponding Author
Email Id: nilamstha255@gmail.com

ABSTRACT

The aim of this study was to formulate and study the effect of different superdisintegrants in etoricoxib dispersible tablet using crospovidone, croscarmellose sodium and sodium starch glycolate as super disintegrants. A direct compression technique was employed to prepare nine different formulations of dispersible tablet by varying the concentration of different super disintegrants in every formulation containing 60mg of etoricoxib, keeping other excipient constant. The powder mixture was evaluated for the pre-compression parameters i.e. bulk density, tapped density, angle of repose, hausner's ratio, carr's index. After the tablets were formulated, the post compression parameters were evaluated i.e. thickness, hardness, weight variation, friability, dispersion time, disintegration time, wetting time, in-vitro dissolution and assay. The prepared dispersible tablets comply all parameter included as per the specification. Among all the formulations, F1, F2 and F3 showed better result (i.e. wetting time, dispersible time, disintegration time, assay, dissolution) in which crospovidone is used as superdisintegrants in comparisons to other superdisintegrants.

Keywords: *Fast dissolving tablets, FDTs, Superdisintegrants, Mouth dissolving tablets, MDTs, drug delivery system, disintegration time.*

INTRODUCTION

Oral route of medicine administration is the most common and favored system of delivery [1] as it's the simplest and easiest way of administering medicines [2]. The route offers ease of medicine administration in an accessible manner and cases are more familiar with this rout. So, patient compliance and therefore medicine treatment is generally more effective with orally given specifics when compared with other routes of administration, for illustration, parenteral [1].

Mouth dissolving tablets are also known as fast dissolving, rapid-fire- dissolving, rapimelt, presto melts, porous tablets, oral dispersible tablets (ODTs), EFVDAS or bouncy medicine immersion system (Elan pot), Orosolv (Cima LabsInc., USA), Zydis (R.P.Scherer, UK). These tablets are generally prepared using snap drying/ lyophilization, tablet molding, and direct compression method.

The US food and Medicine Administration (FDA) center for medicine evaluation and exploration (CDER) defines an ODT in the Orange Book as a solid lozenge form containing medicinal substances, which disintegrates fleetly generally within a matter of seconds, when placed upon the lingo. According to European pharmacopoeia, ODT should dissolve/disintegrate in lower than 3 min [3].

Ideal properties of ODT include dissolution/ decomposition in mouth within seconds in theabsence of water, provides good mouth feel, satisfactory test, harder and less brickle, leave minimum or no residue in mouth after administration [4].

A mouth- dissolving medicine delivery system is a tablet that dissolves or disintegrates in the oral depression without the need of water or chewing. Most fast- dissolving delivery system includes substances to mask the taste of the active component. The masked active component is also swallowed by the case's slaver long with the answerable and undoable excipients. Mouth dissolving tablets are developed by the addition of super disintegrants like cross linked cellulose outgrowth; carboxymethyl cellulose, sodium starch glycolate, polyvinylpyrollidone, which gives burst decomposition when gets in contact with salivary secretion. These are also called melt- in- mouth tablets, porous tablets, oro- dispersible, quick dissolving or rapid-fire disintegrating tablets.

The bioavailability of some medicines may be increased due to immersion of medicines in oral depression and also due to pre-gastric immersion of slaver containing dispersed medicines that pass down into the stomach. Also, the quantum of medicine that's subject to first pass metabolism is reduced as compared to standard tablets [5]. Recent request studies indicate that further than half of the patient population prefers ODTs to other lozenge forms and utmost consumers would ask their croakers for FTDs (70%), purchase FDTs (70%), or prefer FDTs to regular tablets or liquids (>80%) [6].

Ideal Properties of Dispersible Tablets [7]

The ideal properties of fast dissolving tablets are summarized below:

1) Not require water to swallow and should dissolve or disintegrate in the mouth within a few seconds.
2) Allow high drug loading.
3) Be compatible with taste masking and other excipients.
4) Have a pleasing mouth feel.
5) Leave minimal or no residue in the mouth after oral administration.
6) Have sufficient strength to withstand the rigors of the manufacturing process and post manufacturing handling.
7) Exhibit low sensitivity to environmental conditions such as humidity and temperature.
8) Be adaptable and amenable to existing processing and packaging machinery.
9) Allow the manufacture of tablets using conventional processing and packaging equipments at low cost.

Advantages of FTDs [8]

1) Ease of administration to geriatric, pediatric, mentally disabled, and bed-ridden patients, who have difficulty in swallowing the tablet.
2) More convenient for active pharmaceutical ingredients with insufficient stability in water.
3) More easily transportable and they generate less handling and transportation costs for the same amount of active ingredient (less volume, less weight).
4) Can be used in very young children (0 – 6 months).
5) Are easy to dispense and they require minimal manipulation by health professionals and parents prior to use which minimizes the risk of errors.

6) The FDTs do not need water for swallowing unlike conventional dosage forms. This is very convenient for patients who are travelling or do not have immediate access to water, and thus, provide improved patient compliance. Can be dispersed in breast milk.

Disadvantages of FDTs [9]

1) The tablets usually have insufficient mechanical strength. Hence, careful handling is required.
2) The tablets may leave unpleasant taste and/or grittiness in mouth if not formulated properly.
3) Drugs with larger doses are difficult to formulate into FDT

Salient Features of Fast Dissolving Tablets [10,11]

The salient features of fast dissolving tablets are summarized below:

1) Ease of Administration to the patient who cannot swallow.
2) No need of water to swallow the dosage form.
3) Rapid dissolution and absorption of the drug, which will produce quick onset of action.
4) Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach (pre-gastric absorption). In such cases bioavailability of drug is increased and improves clinical performance through a reduction of unwanted effects.
5) Good mouths feel property.
6) The risk of chocking or suffocation during oral administration of conventional formulation due to physical obstruction is avoided.
7) Beneficial in cases such as motion sickness, sudden episodes of allergic attack or coughing, where an ultra-rapid onset of action required.
8) An increased bioavailability, particularly in cases of insoluble and hydrophobic drugs, due to rapid disintegration and dissolution of these tablets.
9) Benefit of liquid medication in the form of solid preparation.
10) Pre-gastric absorption can result in improved bioavailability, reduced dose and improved clinical performance by reducing side effects.
11) Pre-gastric drug absorption avoids the first-pass metabolism; the drug dose can be reduced if a significant amount of the drug is lost through the hepatic metabolism.
12) Rapid drug therapy intervention.
13) New business opportunities: product differentiation, line extension and life-cycle management exclusivity of product promotion and patent-life extension.

Requirements of Fast Dissolving Tablets

Patient Factors [12]

Fast dissolving dosage forms are suitable for those patients (particularly pediatric and geriatric patients) who are not able to swallow traditional tablets and capsules with an 8-oz glass of water. These include the following:

1) Patients who have difficulty in swallowing or chewing solid dosage forms.
2) Patients in compliance due to fear of choking.
3) Very elderly patients of depression who may not be able to swallow the solid dosage forms
4) An eight-year-old patient with allergies desires a more convenient dosage form than antihistamine syrup.
5) A middle-aged patient undergoing radiation therapy for breast cancer may be too nauseous to swallow her H2-blocker.

6) A schizophrenic patient who may try to hide a conventional tablet under his or her tongue to avoid their daily dose of an atypical antipsychotic.
7) A patient with persistent nausea, who may be a journey, or has little or no access to water.

Effectiveness Factor [14]

1) Increased bioavailability and faster onset of action are a major claim of these formulations. Dispersion in saliva in oral cavity causes pre-gastric absorption from some formulate ions in those cases where drug dissolves quickly.
2) Buccal, pharyngeal and gastric regions are all areas of absorption for many drugs. Any pre-gastric absorption avoids first pass metabolism and can be a great advantage in drugs that undergo hepatic metabolism. Furthermore, safety profiles may be improved for drugs that produce significant amounts of toxic metabolites mediated by first-pass liver metabolism and gastric metabolism, and for drugs that have a substantial fraction of absorption in the oral cavity and pre-gastric segments of GIT.

Manufacturing and Marketing Factors [13]

1) As a drug nears the end of its patent life, it is common for pharmaceutical manufacturers to develop a given drug entity in a new and improved dosage form.
2) A new dosage form allows a manufacturer to extend market exclusivity, unique product differentiation and extend patent protection.

For examples, Eisai Inc. launched Aricept FDT, a line extension of donepezil for Alzheimer's disease, in Japan in 2004 and in the U. S. in 2005 in response to a generic challenge filed in the U. S. by Ranbaxy

Challenges to develop FDTs [12, 13]

Palatability

As most drugs are unpalatable, FDTs usually contain the medicament in a taste-masked form. FDTs after administration, it disintegrates or dissolves in patient's oral cavity, thus releasing the active ingredients which come in contact with the taste buds. Hence, taste-masking of the drugs becomes critical to patient compliance.[12,13]

Mechanical strength and Disintegration Time

In order to allow FDTs to disintegrate in the oral cavity, they are made of either very porous and soft-molded matrix or compressed into tablets with very low compression force, which makes the tablets friable and/or brittle, difficult to handle, and often requiring specialized peel-off blister packing that may add to the cost. [12,13] Only wow tab and durasolv technologies can produce tablets that are sufficiently hard and durable to allow them to be packaged in multi-dose bottles.[12]

Hygroscopicity

Several orally disintegrating dosage forms are hygroscopic and cannot maintain physical integrity under normal conditions of temperature and humidity. [12,13]
Hence, they need protection from humidity which calls for specialized product packaging. [12]

Amount of Drug

The application of technologies used for FDTs is limited by the amount of drug that can be incorporated into each unit dose. For lyophilized dosage forms, the drug dose must be less

than 400 mg for insoluble drugs and 60 mg for soluble drugs. This parameter is particularly challenging when formulating a fast-dissolving oral films or wafers. [12,13]

Aqueous Solubility

Water-soluble drugs pose various formulation challenges because they form eutectic mixtures, which result in freezing-point depression and the formation of a glassy solid that may collapse upon drying because of loss of supporting structure during the sublimation process [12,13,14]. Such collapse sometimes can be prevented by using various matrix-forming excipients such as mannitol that can induce crystallinity and hence, impart rigidity to the amorphous composite [12].

Size of Tablet

The ease of administration of a tablet depends on its size. It has been reported that the easiest size of tablet to swallow is 7-8 mm while the easiest size to handle was one larger than 8 mm. Therefore, the tablet size that is both easy to take and easy to handle is difficult to achieve [12,14].

Mouth Feel

FDTs should not disintegrate into larger particles in the oral cavity. The particles generated after disintegration of the FDTs should be as small as possible. Moreover, addition of flavours and cooling agents like menthol improve the mouth feel [14].

Sensitivity to Environmental Conditions

FDTs should exhibit low sensitivity to environment conditions such as humidity and temperature as most of the materials used in FDTs are meant to dissolve in minimum quantity of water [14].

Criteria for excipient used in formulation of FDTs [14,15,16]

1) Their individual properties should not affect the FDTs.
2) It must be able to disintegrate quickly.
3) It should not have any interaction with drug and other excipients.
4) When selecting binder (a single or combination of binders) care must be taken in the final integrity and stability of the product.
5) The melting point of the excipients used should be in the range of 30-35 °C.
6) It should not interfere in the efficacy and organoleptic properties of the product.
7) The binder may be in liquid, semi-solid, solid or polymeric in nature.

Excipients used in FDT Preparation

Excipients used in FDTs contain at least one super disintegrant, a diluent, a lubricant and optionally a swelling agent, a permeabilizing agent, sweeteners and flavouring agents.

Name and Weight Percentage of Various Excipients in FDTs [17,18]

S. No.	Name of the excipients	% used
1.	Superdisintegrants	1-15%
2.	Binders	5-10%
3.	Antistatic agent	0-10%
4.	Diluents	0-85%

List of super disintegrants [14,19]

S. No.	Superdisintegrant	Mechanism of action	Specific properties
1.	Croscarmellose Sodium	Swells 4–8 folds in<10 Combination of swelling andwicking action. Swells 7–12 folds in<30 s. s	Swelling and wicking action Effective in low concentration (0.5–2.0%), high swelling capacity, cross-linking of the carboxyl ester groups.
2.	Crospovidone	Combination of swelling and wicking action. Swells 7–12 folds in<30 s.	The effective concentration is 1–3%. Rapidly disperses and swells in water, available in micronized grades.
3.	Cross-linked alginic acid	Hydrophilic colloidal subs-tancewhich has high sorption capacity.	The combination of swelling and wicking action causes disintegration.
4.	Gellatin gum	Strong swelling properties upon contact with water.	Anionic polysaccharide of linear tetrasaccharides, good superdisintegrants property similar to the modified starch and celluloses.
5.	Sodium starch glycolate	Strong swelling properties upon contact with water. Swells 7–12 folds in<30s.	Rapid absorption of water results in swelling up to 6%, high concentration causes gelling.
6.	Soy polysaccharide	Rapid dissolving	Doesnot contain starch or sugar so can be used in products meant for diabetics.
7.	Xanthan gum	Extensive swelling prop-erties for faster disintegration.	High hydrophilicity and low gelling tendency, low water solubility.

Bulking Materials [19,20]

1) Bulking materials are important in the development of fast dissolving tablets. They contribute the functions of a diluent, filler and cost reducer. Bulking agents improve the texture of the tablets that consequently enhances the disintegration in the mouth, besides adding volume and reducing the concentration of the active in the formulation. The bulking agents for this dosage form should be more sugar-based such as mannitol, polydextrose, lactose derivatives such as directly compressible lactose (DCL) and starch hydrolysate for higher aqueous solubility and good sensory perception. Mannitol especially has high aqueous solubility and good sensory perception, as it provides a cooling effect due to its negative heat of solution. Bulking agents are added in the range of 10% to about 90% by weight of the final composition.
2) The descending order of brittleness of excipients is ranked as microcrystalline cellulose>alpha lactose monohydrate>spray-dried lactose>anhydrous beta lactose>anhydrous alpha lactose>> dicalcium phosphate dihydrate.
3) The commonly used sugar-based excipients are especially bulking agents (like dextrose, fructose, lactitol, maltitol, maltose, mannitol, sorbitol, starch hydrolysate, polydextrose

and xylitol) which exhibit high aqueous solubility and sweetness thereby contribute taste masking property and provide pleasant mouth feel. Sugar based excipients can be of types on the basis of moulding and dissolution rate:

4) Type 1 saccharides: (lactose and mannitol) which exhibit low moldability but high dissolution rate.
5) Type 2 saccharides: (maltose and maltitol) which exhibit high moldability but low dissolution rate.

Emulsifying Agents [14,19]

Emulsifying agents are significant for formulating fast dissolving tablets as they help in quick disintegration and drug release without the need for chewing, swallowing or drinking water. Also, emulsifying agents stabilize the immiscible blends and increase bioavailability. A variety of emulsifying agents for fast dissolving tablet formulations include alkyl sulfates, propylene glycol esters, lecithin, sucrose esters and others. These can be added in the range of 0.05% to about 15% by weight of the final formulation.

Lubricants [14,21]

Though not essential excipients, these can aid in making the tablets more palatable after they disintegrate in the mouth. Lubricants reduce grittiness and help in the drug transit process from the oral to the stomach.

Flavours (taste masking agents) and Sweeteners [14, 19]

Flavours and taste masking agents make the products more palatable and pleasing for patients. The incorporation of these ingredients assists in overcoming bitterness and undesirable tastes of some actives. Natural as well as synthetic flavours can be used to enhance the organoleptic characteristic of fast dissolving tablets. A wide range of sweeteners including sugar, dextrose and fructose, as well as non-nutritive sweeteners such as aspartame, sodium saccharin, sugar alcohols and sucralose are available. The addition of sweeteners imparts a pleasant taste as well as bulk to the formulation.

Mechanism of action of disintegrants [22,23]

There are five major mechanisms for tablet disintegration as follows: -

1) Swelling
2) Porosity and Capillary Action (Wicking)
3) Deformation
4) Enzymatic reaction
5) Due to disintegrating particle/particle repulsive forces

Swelling

Swelling is believed to be a mechanism in which certain disintegrating agents (such as starch) impart the disintegrating effect. By swelling in contact with water, the adhesiveness of other ingredients in a tablet is overcome causing the tablet to fall apart.

E.g. Sodium starch glycolate, *PlatagoOvata.*

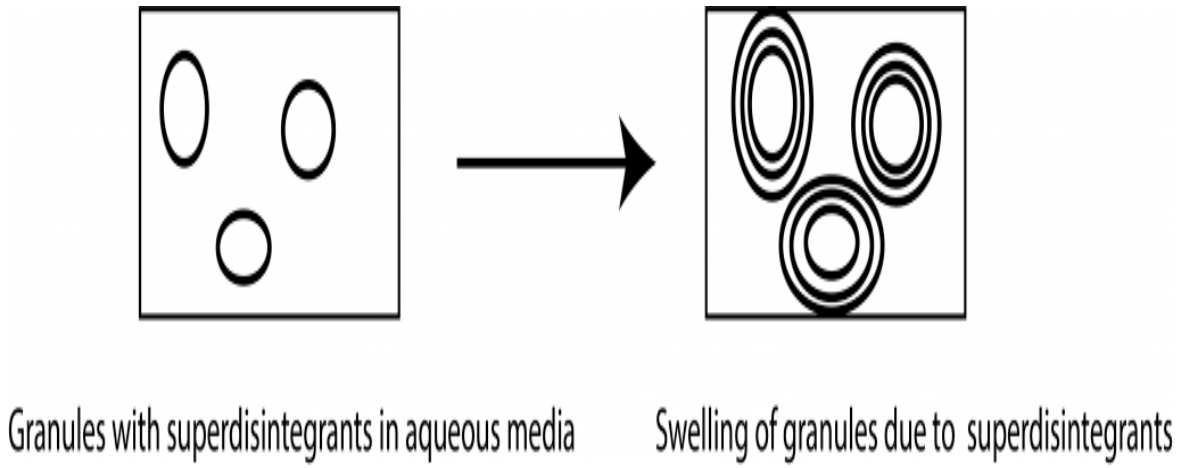


Fig. 1: Disintegration by swelling

Porosity and Capillary Action (Wicking)

Effective disintegrants that do not swell are believed to impart their disintegrating action through porosity and capillary action. Tablet porosity provides pathways for the penetration of fluid into tablets. The disintegrants particles (with low cohesiveness & compressibility) themselves act to enhance porosity and provide these pathways into the tablet. Liquid is drawn up or "wicked" into these pathways through capillary action and rupture the interparticulate bonds causing the tablet to break apart. E.g. Crospovidone, Croscarmellose Sodium.

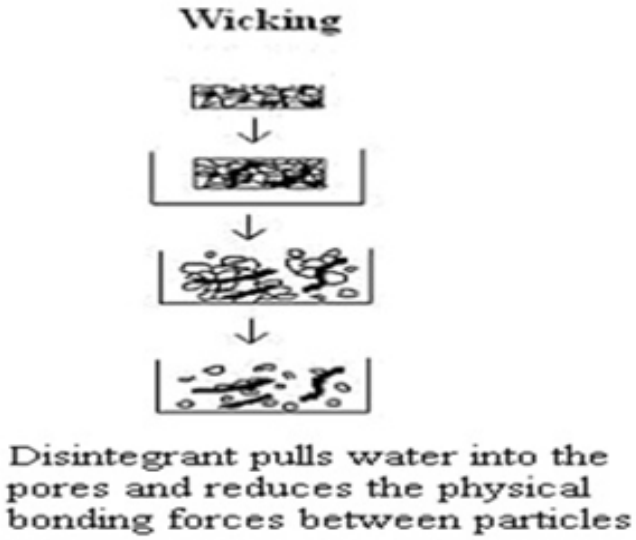


Fig. 2: Disintegration by wicking

Deformation

Starch grains are generally thought to be "elastic" in nature meaning that grains that are deformed under pressure will return to their original shape when that pressure is removed. But, with the compression forces involved in tableting, these grains are believed to be deformed more permanently and are said to be "energy rich" with this energy being released upon exposure to water. In other words, the ability for starch to swell is higher in "energy rich" starch grains than it is for starch grains that have not been deformed under pressure.

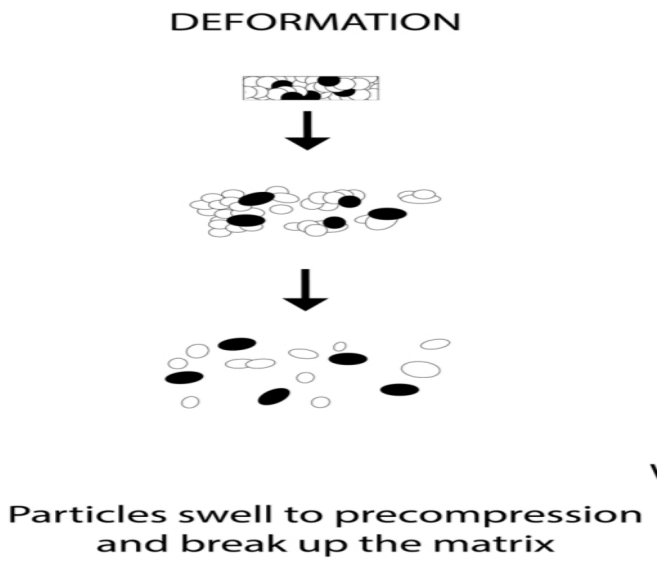


Fig. 3: Disintegration by deformation

Enzymatic Reaction

Enzymes present in the body also act as disintegrants. These enzymes dearth the binding action of binder and helps in disintegration. Due to swelling, pressure is exerted in the outer direction that causes the tablet to burst or the accelerated absorption of water leads to an enormous increase in the volume of granules to promote disintegration.

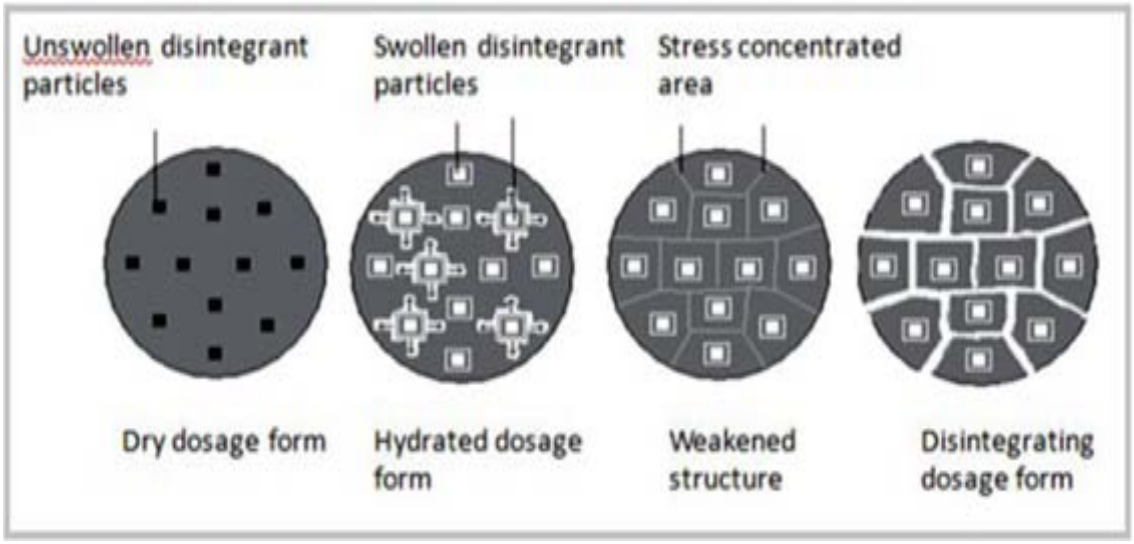


Fig. 4: Disintegration by enzyme reaction

Due to Disintegrating Particle/Particle Repulsive Forces

Another mechanism of disintegration attempts to explain the swelling of tablet made with "non-swellable" disintegrants. Guyot-Hermann has proposed a particle repulsion theory based on the observation that non-swelling particle also cause disintegration of tablets. The electric repulsive forces between particles are the mechanism of disintegration and water is required for it. Researchers found that repulsion is secondary to wicking. It is believed that no single mechanism is responsible for the action of most disintegrants. But rather, it is more likely the result of inter-relationships between these major mechanisms.

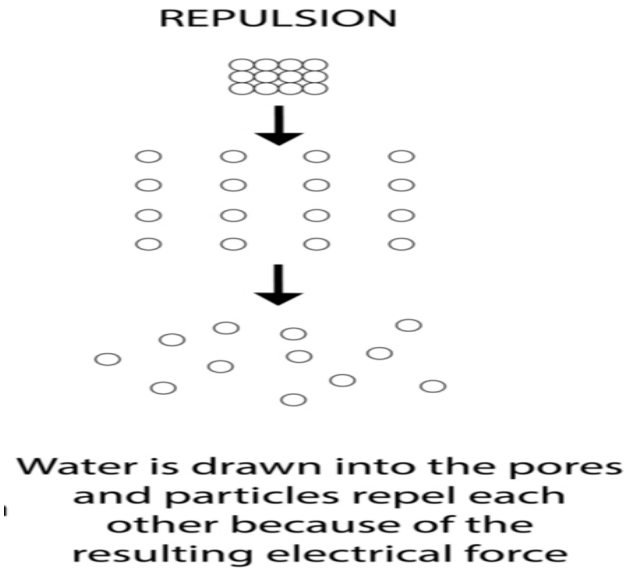
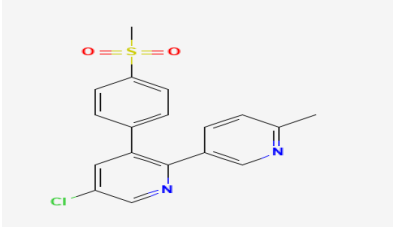


Fig. 5: Disintegration by repulsion

Drug Profile[24]

Name	Etoricoxib
Synonyms	Etoricoxibum 5-chloro-2-(6-methylpyridin-3-yl)-3-(4-(methylsulfonyl)phenyl)pyridine
IUPAC Name	5-chloro-3-(4-methanesulfonylphenyl)-2-(6-methylpyridin-3-yl)pyridine
Trade name	Arocox, E-Cox, Ezact, Nucoxia
Molecular formula	$C_{18}H_{15}ClN_2O_2S$
Molecular weight	358.842
Dose	60mg
Type	Small Molecule
Groups	Approved, Investigational
Structure	

Pharmacology

Indication	Osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, chronic low back pain, acute pain and gout.
Pharmacodynamics	Etoricoxib is a COX-2 selective inhibitor (approximately 106 times more selective for COX-2 inhibition over COX-1).
Mechanism of action	Like any other COX-2 selective inhibitor Etoricoxib selectively inhibits isoform 2 of cyclo-oxigenase enzyme (COX-2), preventing production of prostaglandins (PGs) from arachidonic acid.
Absorption	Bioavailability is 100% following oral administration.

Metabolism	Hepatic, CYP extensively involved (mainly CYP3A4)
Protein binding	92%
Half life	22 hours
Adverse effect	Abdominal pain, Headache, indigestion, heartburn, diarrhoea, skin rashes, nausea and vomiting.
Contraindications	Contraindicated in patients with severe ulcer, gastrointestinal bleeding, hypersensitivity and pregnancy.
Drug Interaction	Lithium, Digoxin, Corticosteroids, antihypertensives

Technologies for Preparing of Fast Dissolving Tablets [11, 25]
Several technologies are available for preparing fast dissolving tablets. The available technologies are presented in Table 1 and summarized below.

List Technologies for Preparing of Fast Dissolving Tablets

Conventional technologies	Patented technologies
1. Freeze drying	1. Zydus technology
2. Sublimation	2. Orasolv technology
3. Spray drying	3. Durasolv technology
4. Moulding	4. Wowtab technology
5. Mass extrusion	5. Flashdose technology
6. Direct compression	6. Flashtab technology
7. Cotton-candy process	7. Shear form Technology
8. Nanotization	8. Ceform technology

Freeze Drying or Lyophilization

Sublimation

This process involves addition of other excipients and the compression of blend into tablet. Removal of volatile material by sublimation creates pores in tablet structure, due to which tablet dissolves when comes in contact with saliva. Additionally, several solvents like cyclohexane, benzene etc. can also be used as pore forming agents. Mouth dissolving tablets with highly porous structure and good mechanical strength have been developed by this method.

Spray Drying

A highly porous and fine powder is prepared by spray drying an aqueous composition containing support matrix and other components. This is then mixed with active ingredient and compressed into tablet. Spray drying is widely used in pharmaceutical and biochemical fields and the final particle size is controlled by a number of factors including the size of the nozzle used in the processing. FTD prepared from spray drying disintegrates within 20 seconds when immersed in an aqueous medium.

Molding

Tablets produced by molding are solid dispersions. Physical form of the drug in the tablets depends whether and to what extent, it dissolves in the molten carrier. The drug can exist as discrete particles or micro particles dispersed in the matrix. It can dissolve totally in the

molten carrier to form solid solution or dissolve partially in the molten carrier and the remaining particles stay undissolved and dispersed in the matrix.

Mass Extrusion

In this technique, a blend of active drug and other ingredients is softened using solvent mixture of water-soluble polyethylene glycol, using methanol and then the softened mass is extruded through the extruder or syringe to get a cylinder of product, which is finally cut into even segments with the help of heated blades to get tablets. The dried cylinder can be used to coat the granules of bitter tasting drugs and thereby masking their bitter taste.

Direct Compression

The disintegrant addition technology (direct compression) is the most preferred technique to manufacture the tablets. The advantages of direct compression method are summarized below:

1) High doses can be accommodated and final weight of the tablet can exceed that of other methods.
2) Easiest way to manufacture the FDT tablets.
3) Conventional equipment and commonly available excipients are used.
4) A limited number of processing steps are involved
5) Cost-effectiveness.

Cotton Candy Process

This process is so named as it utilizes a unique spinning mechanism to produce floss-like crystalline structure, which mimic cotton candy. Cotton candy process involves formation of matrix of polysaccharides or saccharides by simultaneous action of flash melting and spinning. The matrix formed is partially recrystallized to have improved flow properties and compressibility. This candy floss matrix is then milled and blended with active ingredients and excipients and subsequently compressed to ODT.

Nanonization

In this process, the particles of the drug are reduced in size to nano particles by milling the drug in the proprietary wet milling process. The agglomeration can be prevented by surface adsorption of the nanocrystals. These are then compressed and changed into a tablet. This technique is very useful for less water-soluble drugs. The bioavailability of the drug is increased as the disintegration time is reduced to a significant extent.

Flashtab Technology

Prographarm labs have a patent over this technology. In this technology, micro granules of the taste- masked active drug are used. These may be prepared by using conventional techniques like coacervation, microencapsulation, and extrusion spheronisation. All these processes utilize conventional tableting technology

MATERIALS AND METHODS

Materials

The active ingredient Etoricoxib was received as a gift sample from Deurali Janta Pharmaceuticals Pvt Ltd. Sodium starch glycolate, Cross Povidone and Cross carmellose sodium are the super disintegrants received as gift samples from CTL Pharmaceuticals Pvt

Ltd. and Nova Genetica Pharmaceuticals Pvt Ltd. All the other ingredients used in the formulation are of pharmaceutical analytical grade.

Equipments/instruments: The equipment used in this project are presented in Table 1.

Table 1: List of Equipment, Instrument and Machineries used.

S. N.	Instrument	Manufacturer
1	Dissolution Test Apparatus	Aastha International/PDA-65
2.	Digital Electronic balance	Kern & Sohn GmbH/D- 72335
3.	Friability test apparatus	Dica India® /FTA-23/D
4.	Tablet hardness tester	Monsanto type
5.	UV spectrophotometer (double beam)	ELICO®/SL210UV SPECTROPHOTOMETER
6.	Disintegration test apparatus	EI/1209578
7.	pH Meter	Simtronics®
8.	Bulk density apparatus	Dica India
9.	Digital Vernier caliper	Stainless Hardened
10.	Glass wares	Borosilicate Grade
11.	8 station rotatory tablet punching machine	Cemech machineries Ltd/R & D labpress

METHODOLOGY

Pre-formulation Study

Pre-formulation studies relates to pharmaceutical and analytical investigation carried out proceeding and supporting formulation development efforts of the dosage form of the drug substance. It gives information needed to define the nature of drug substance and provide framework for the drug combination with pharmaceutical excipients in the dosage form. Hence, following pre-formulation studies were performed.

Determination of solubility

The solubility of etoricoxib was performed in solvents water, methanol, acetone, ether.

Determination of λ_{max}

A solution of etoricoxib containing conc. 10µg/ml was prepared in methanol and UV spectrum was taken using spectrophotometer. The solution was scanned in the range of 200-400 nm.

Preparation of Standard Calibration Curve for Etoricoxib

Accurately weighed 50mg of etoricoxib was dissolved in Methanol and volume was made up to 100 ml by methanol. From this stock solution, 1ml was pipette and added to 10ml V.F and volume was made 10 ml with methanol. Similarly, from the Stock solution different aliquot of 30, 40, 50, 60 and 70 µg/ml were prepared respectively. Then, the absorbance was measured at 238 nm using UV Spectrophotometer. The standard curve was obtained by plotting absorbance versus concentration in µg/ml.

Formulation Development

Etoricoxiboro dispersible tablets were manufactured in nine formulations F1 to F9 using the ingredients mentioned in the Table keeping the total weight (350mg) of the tablet constant in

all the formulations. An excipient (diluent, superdisintegrants, sweetener, flavouring agent,) were passed through sieve #60 and active drug was passed through the sieve #44. Magnesium stearate and talc was passed through sieve #100 and mixed with the above blend for sufficient time (in an air tight plastic container). And mixtures were compressed by direct compression method.

Formulation of Etoricoxib

Nine batch of etoricoxib tablets were prepared using the formulation shown in Table 2.

Table 2: Formulation Chart of Etoricoxib Mouth Dissolving Tablets. (F1-F9)

Ingredients (mg)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Etoricoxib	60	60	60	60	60	60	60	60	60
Crospovidone	10	20	30	-	-	-	-	-	-
Croscarmellose Sodium	-	-	-	10	20	30	-	-	-
Sodium starch glycolate	-	-	-	-	-	-	10	20	30
Lactose	60	60	60	60	60	60	60	60	60
Microcrystalline cellulose	70	70	70	70	70	70	70	70	70
Talc	10	10	10	10	10	10	10	10	10
Magnesium stearate	10	10	10	10	10	10	10	10	10
Flavor (lemon)	3	3	3	3	3	3	3	3	3
Saccharin	6	6	6	6	6	6	6	6	6
Mannitol	121	111	101	121	111	101	121	111	101
Total weight	**350**	**350**	**350**	**350**	**350**	**350**	**350**	**350**	**350**

Evaluations of Oro Dissolving Tablet [26, 27, 28]

Pre- Compression Parameters

The following pre-compression evaluation were performed.

Bulk Density

Bulk density was determined by pouring the blend into a graduated cylinder. A quantity of 10g of powder from each formulation, previously lightly shaken to break any agglomerates formed was introduced into a 50ml measuring cylinder. The bulk volume and mass of the powder was determined. The bulk density was calculated byusing below formula.

$$\text{Bulk density} = \frac{mass\,of\,powder}{bulk\,volume\,of\,powder}$$

Tapped Density

The measuring cylinder containing known mass of blend was tapped for fixed time. The minimum volume occupied in the cylinder and the mass of the blend was measured. The tapped density was calculated using the following formula.

$$\text{Tapped density} = \frac{mass\,of\,powder}{tapped\,volume\,of\,powder}$$

Carr's Index

The simplest way for measurement of free flow of powder is compressibility, an indication of ease with which a material can be induced to flow is given by Carr's index which is calculated as follow.

Carr's index (%) = [(TD-BD)/TD]*10

Table 3: For the Compressibility Index, The Generally Accepted Scale of Flow Ability

Flow Character	Compressibility Index
Excellent	≤ 10
Good	11-15
Fair	16-20
Passable	21-25
Poor	26-31
Very poor	32-37
Very, very poor	>38

Angle of Repose

The powder mixture was taken in a funnel. The height of the funnel was adjusted at definite height in such a way that the tip of the funnel just touches the apex of the heap of blend. The drug blend was allowed to flow through the funnel freely on to the surface. The diameter of the powdered cone was measured and the angle of repose was calculated using the following equation:

$$\text{Tan } \theta = \frac{h}{r}$$

Where, θ = Angle of repose
h = height of the cone
r = Radius of the cone

Table 4. Showing Flow Property for Angle of Repose

Flow Property	Angle of Repose (degree)
Excellent	25-30
Good	31-35
Fair	36-40
Passable	41-45
Poor	46-55
Very poor	56-65
Very, very poor	>66

Hausner Ratio

It is the ratio of tapped density to its bulk density and can be applied to provide an index of the flow character of a powder.

Hausner Ratio = Tapped density / Bulk density

Table 5. Showing Flow Property Hausner Ratio

Hausner ratio	Flow ability
1.00-1.11	Excellent
1.12-1.18	Good
1.19-1.25	Fair
1.26-1.34	Passable
1.35-1.45	Poor
1.46-1.59	Very poor
>1.60	Very very poor

Post-compression Parameters [29]

Physical Characterization of tablets

Twenty tablets were randomly selected from the prepared formulation and examined for shape, thickness and diameter.

Weight Variation

As per IP specifications to perform test for uniformity of weight twenty tablets from each formulation were selected randomly and their average weights were calculated. Percentage weight differences were calculated and checked with IP specifications.

Table 6. Showing Range of Weight Variation as their Tablet Weight in mg

Average weight of tablet (%)	% Deviation
80mg or less	±10
80mg to 250mg	±7.5
250mg or more	±5

Tablet Thickness

The thickness of tablet was measured by placing the tablet between two arms of the digital vernier caliper 5 tablets were taken and their thickness was measured.

Tablet hardness

The tablet hardness, which is the force required to break a tablet in diametric compression force. The hardness tester used in the study was Monsanto hardness tester, which applies force to the tablet diametrically with the help of an inbuilt spring.

Friability Test

The friability of the tablets was measured in a Roche friabilator. Tablets of a known weight (W_o) or a sample of 20 tablets are dedusted in a drum for a fixed time (100 revolutions) and weighed (W1) again. Percentage friability was calculated from the loss in weight as given in equation as below. The weight loss should not be more than 1%.

$$\textbf{Friability (\%)} = \frac{\text{Initial weight(Wo)} - \text{Final weight(W1)}}{\text{Inital weight(Wo)}} \times 100\%$$

Wetting Time

A piece of tissue paper (12cmx10.75cm) folded twice was placed in a petri dish (internal diameter= 9cm). 10ml of water containing Eosin, a water-soluble dye, was added to petri dish. A tablet was placed carefully on the surface of tissue paper. The time required for water to each upper surface of the tablet was noted as a wetting time.

Dispersion Time
Tablet was added to 15 ml of water and time required for complete dispersion was measured. Three tablets from each formulation were randomly selected and dispersion time was performed.

Disintegration Time
The test was carried out on 6 tablets using Tablets disintegration tester, distilled water at 25ºC± 2ºC was used as a disintegration media and the time taken for complete disintegration of the tablet with no passable mass remaining in the apparatus was measured in seconds.

Wetting time
A piece of tissue paper (12cmx10.75cm) folded twice was placed in a petri dish (internal Diameter = 9cm). 10ml of water containing Eosin, a water-soluble dye, was added to petri-dish. A tablet was placed carefully on the surface of tissue paper. The time required for water to each upper surface of the tablet was noted as a wetting time. 3 tablets of each formulation were taken for the determination of wetting time.

Water Absorption Ratio
A tablet was weight and was placed in the petridish containing 6 ml of phosphate buffer with tissue paper placed on it. When tablet absorbs the buffer solution completely then it was removed and weight. Water absorption can be calculated as:
Water absorption ratio = (final weight – Initial weight / Initial weight) X 100%

Dispersion Time
Tablet was added to 15 ml of water and time required for complete dispersion was measured. Three tablets from each formulation were randomly selected and dispersion time was performed.

Disintegration Time
The test was carried out on 6 tablets using Tablets disintegration tester, distilled water at 25ºC± 2ºC was used as a disintegration media and the time taken for complete disintegration of the tablet with no passable mass remaining in the apparatus was measured in seconds.

In vitro Drug release [30]

Preparation of Standard
Accurately 66 mg standard etoricoxib was weighed and transferred to 100 ml volumetric flask (VF). Drug was dissolved in phosphate buffer pH 7.0 and volume was made up to by phosphate buffer pH 7.0.

Preparation of Sample
In-vitro drug release of the samples was carried out using USP – type II dissolution apparatus (paddle type). The dissolution medium, 900 ml of buffer solution, was placed into the dissolution flask maintaining the temperature of 37±2ºC and of 50 RPM. Six tablets were placed in each flask of dissolution apparatus. The apparatus was allowed to run for 10 min. Samples measuring 10 ml were taken out in 10 minutes. The collected samples were analysed at 238 nm using dissolution medium as blank. The percentage drug release was calculated. The details of the in-vitro dissolution study are presented in Table 3.6.

Table 7. *In Vitro* Dissolution Studied Detail

Apparatus used	USP type II dissolution apparatus
Dissolution medium	Phosphate buffer pH 7.0
Dissolution medium volume	900 ml
Temperature	37±2ºC
Speed of paddle	50 rpm
Sample withdrawn	10 ml
Sample withdrawn	238 nm

Assay [30]

Preparation of Standard

Accurately 50 mg standard etoricoxib was weighed and transferred to 100 ml volumetric flask (VF). Drug was dissolved in methanol and volume was made up to the 100ml and from that 1ml was taken out and volume was made up to 10ml by methanol.

Preparation of Sample

Five tablets from each formulation were weighted and crushed in a motor. Powder equivalent to 50mg etoricoxib was taken and transferred in 100ml of volumetric flask. Powder was dissolved in methanol with the aid of ultrasound. The solution was filtered then 1ml of filtrate was further diluted to 10ml with methanol and analyzed spectrophotometrically at 238 nm.

Procedure

The absorbance was measured at 238nm to find out the content of etoricoxib. Content of etoricoxib in tablet in percentage was calculated by using following formula.

$$(\%) = \frac{\text{absorbance of sample}}{\text{absorbance of standard}} \times \frac{\text{weight of standard}}{\text{weight of sample}} \times \text{dilution} \times \frac{\text{average weight}}{\text{label claim}} \times 100\%$$

RESULTS

Authentication of Drugs

Determination of Solubility

Solubility studies were carried out in different solvents and observations are presented in table 4.1

Table 8. Solubility Profile of Etoricoxib

Solvent	Solubility
Methanol	Soluble
Acetone	Soluble
Chloroform	Freely soluble
Water	Partially soluble
Ethanol	Sparingly soluble
Tetrahydrofuran	Freely soluble

Determination of λmax of etoricoxib

λmax of etoricoxib was found to be 238 nm. The result is plotted as shown in Figure 6.

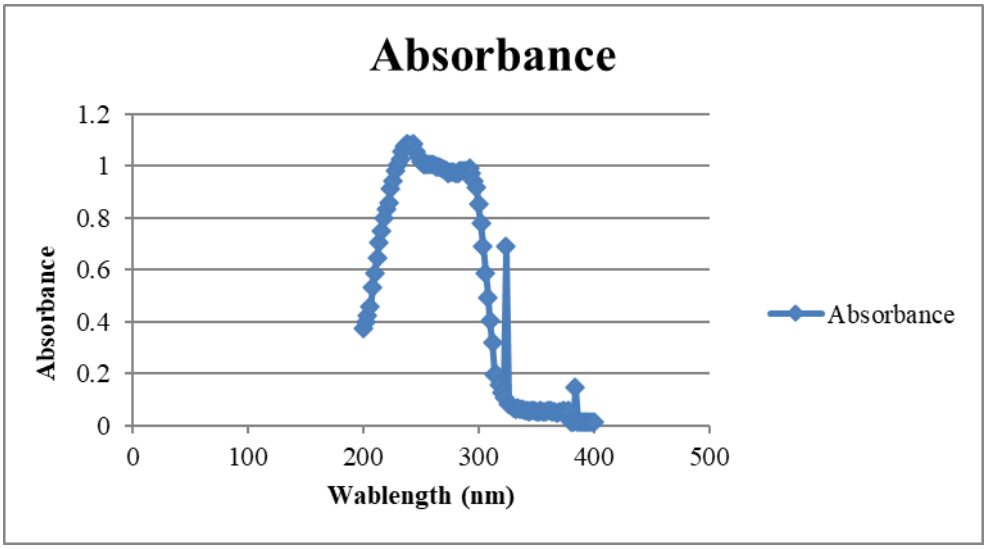


Fig. 6. Standard Calibration Curve of Etoricoxib

A Standard Calibration Curve for etoricoxib was obtained by measuring absorbance at 238 nm and by plotting graph of absorbance vs concentration. The absorbance reading of etoricoxib were showed in Table 9.

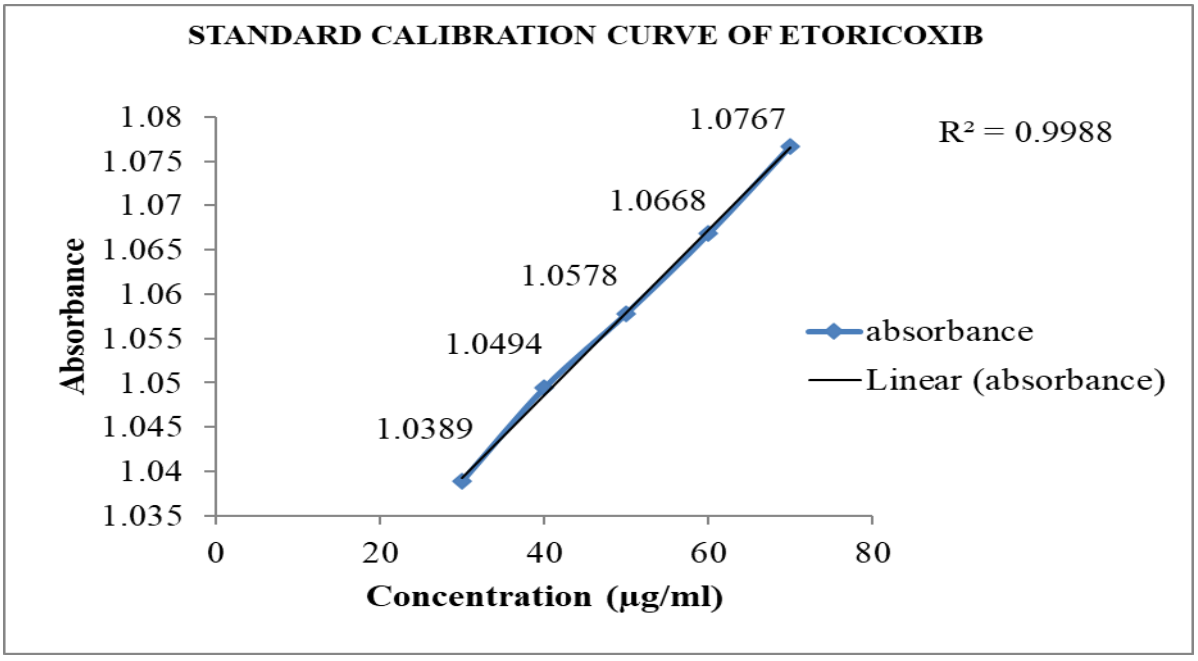


Fig. 7. Standard Calibration Curve of Etoricoxib

Table 9: Absorbance of etoricoxib at different concentration for calibration

Concentration (µg/ml)	Absorbance (238nm)*	R2 value
30	1.0389	0.9988
40	1.0494	
50	1.0578	
60	1.0668	
70	1.0767	

Pre-compression Parameter

Pre-compression parameter including bulk density, tapped density, compressibility index, angle of repose and Hausner's Ratio are presented in Table 9.

Table 10. Pre-Compression Parameters

Formulation code	Bulk Density (g/cm^3)	Tapped Density (g/cm^3)	Compressibility index (%)	Hausner's Ratio	Angle of repose(θ)
F1	0.5	0.625	20	1.25	29.53
F2	0.5	0.667	25	1.33	32.73
F3	0.49	0.625	21.56	1.275	26.5
F4	0.5	0.609	18	1.219	28
F5	0.49	0.667	26.47	1.36	33
F6	0.5	0.625	20	1.25	32
F7	0.5	0.625	20	1.25	26
F8	0.5	0.617	19	1.234	36
F9	0.5	0.724	31	1.45	31

Table 11. Showing Post Compression Parameters

Post-Compression Parameters

Hardness, Friability, Disintegration time, Wetting time, Dispersion time and Weight Variation.

Formulation code	Thickness (mm)	Hardness (Kg/cm^2)	Friability %	Disintegration time (sec)	Wetting time (sec)	Dispersion time (sec)
F1	3.4	4.93	0.429	20	12	25
F2	3.5	5.76	0.3149	18	9	21
F3	3.5	5.5	0.272	17	7	21
F4	3.3	4.9	0.386	45	30	80
F5	3.2	4.8	0.401	18	13	42
F6	3.2	5.1	0.401	55	20	58
F7	3.3	5.125	0.357	51	19	61
F8	3.2	5.5	0.315	54	22	64
F9	3.3	5.2	0.457	51	17	65

Assay of Formulated Batches

Table 12 for Assay *In-vitro* drug release

Formulation code	Assay %
F1	101.6
F2	99.22
F3	102.8
F4	100.1
F5	97.18
F6	97.9
F7	99.72
F8	99
F9	103.3

Table 13. Cumulative Drug Release

Formulation	% Drug Release in 10 min
F1	98.18
F2	100.83
F3	101.24
F4	98.4
F5	99.72
F6	98.12
F7	99.82
F8	98.40
F9	99.6

DISCUSSION

Pre compression Parameters

Pre compression parameters play an important role in improving the flow properties of pharmaceuticals especially in tablet formulation. These include angle of repose, bulk density, tapped density Hausners ratio and Carr's index. Before formulation of tablets the drug was evaluated for all the above said parameters and it was found that all the observations were within the prescribed limits of IP.

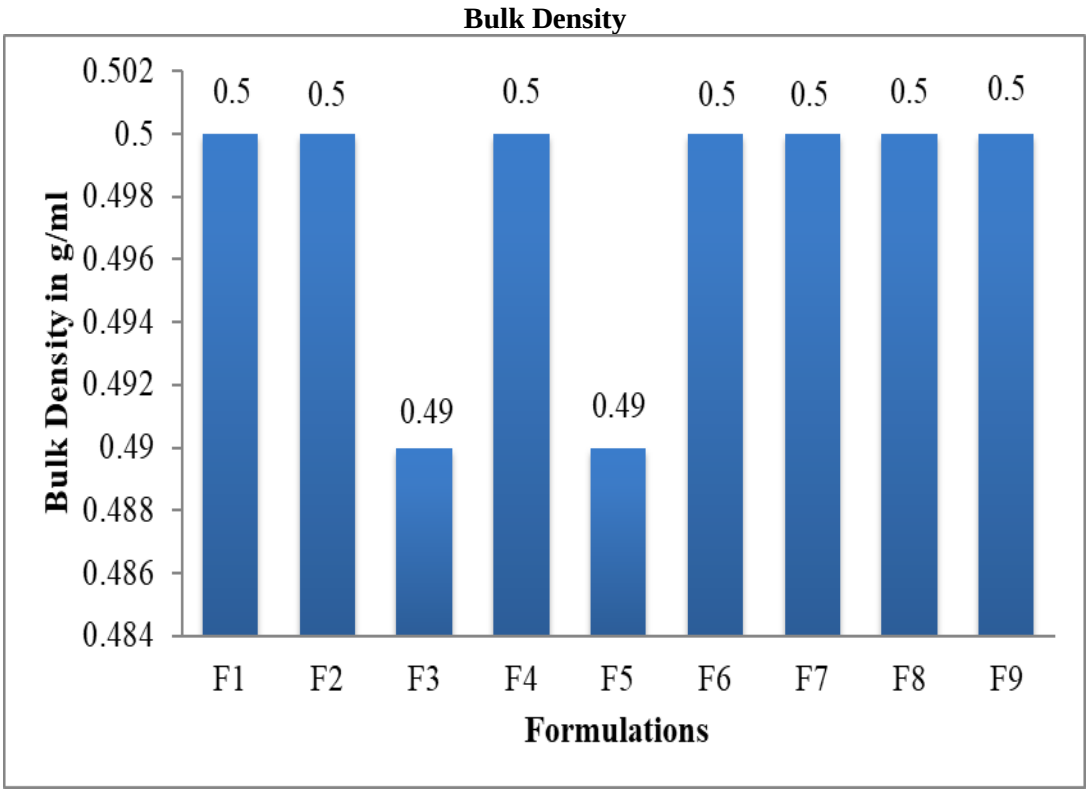


Fig 8. Bar chart for Bulk density

The value of bulk density of all formulation prepared fall within the range of 0.49-0.5 g/cm³.

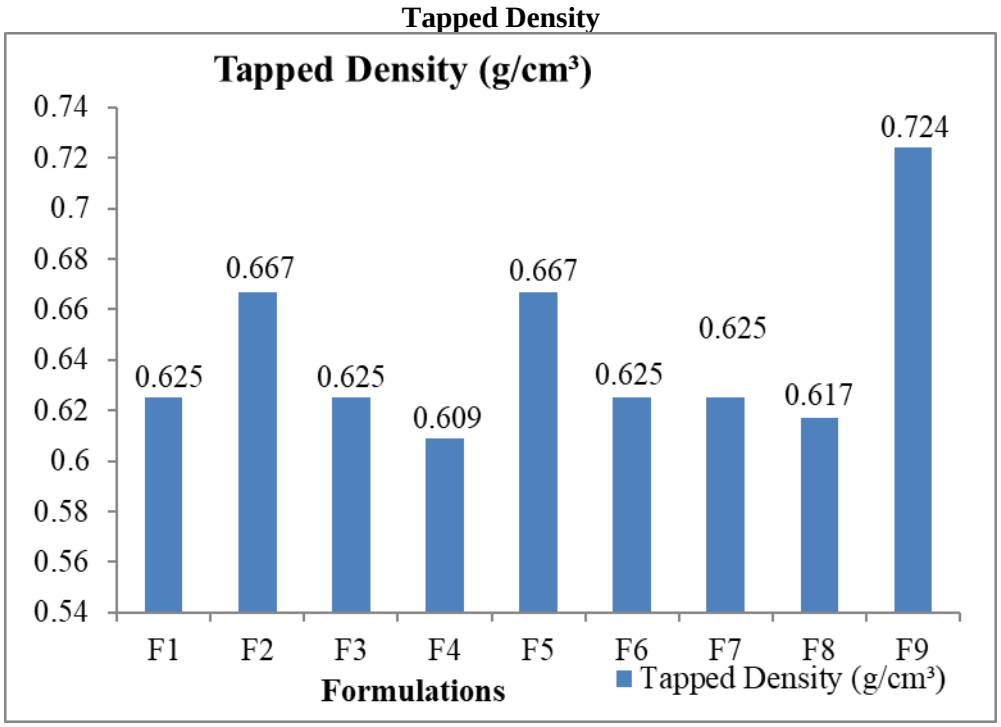


Fig. 9. Bar chart for Tapped density

It was found that the value of tapped density of all the formulation range from 0.609-0.724g/cm^3.

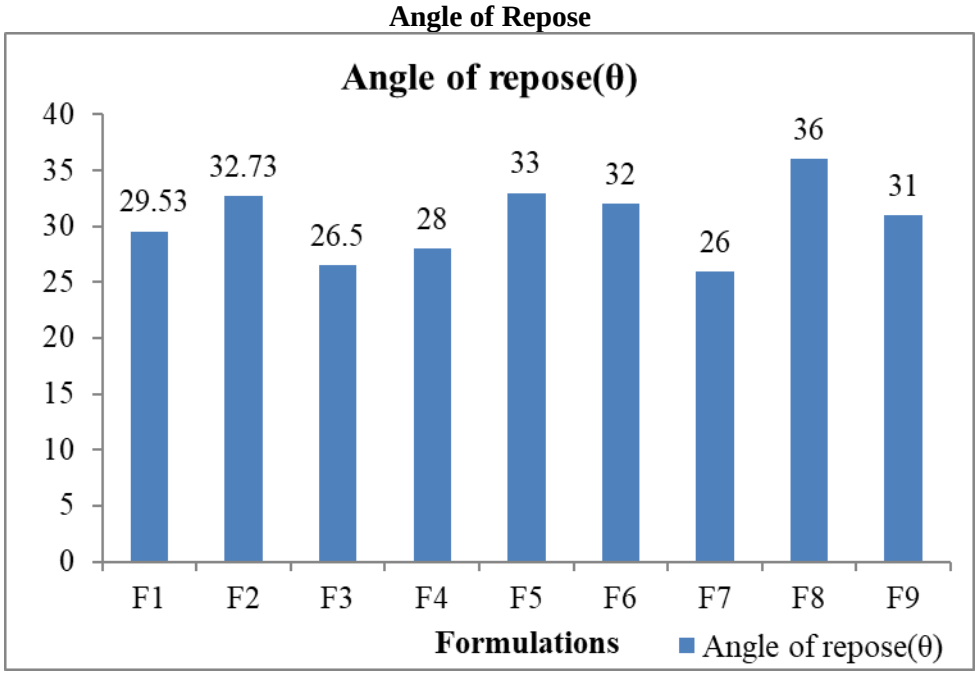


Fig. 10. Bar chart for Angle of repose (in degree)

Since, the angle of repose of powder from all formulation was determined. The formulation F1, F3, F4 and F7 showed excellent flow character. The formulation F2, F5, F6 and F9 were good flow character and F8 were fair flow character.

Carr's Index/ Compressibility Index

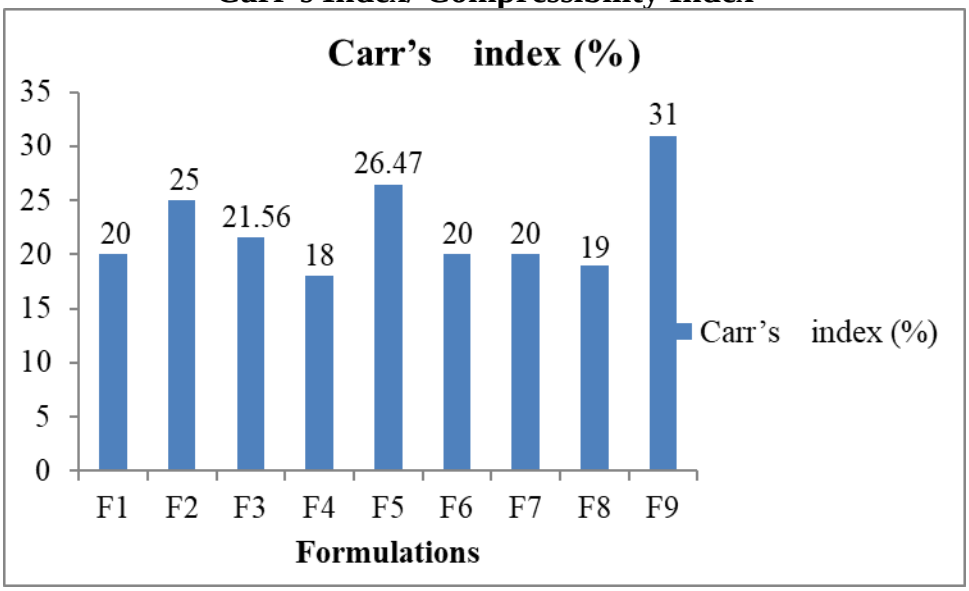


Fig. 11. Bar chart for Carr's index (%)

Since, carr's index of all formulation was determined. The formulation F1, F4, F6, F7and F8 showed fair flow character. The formulation F2, and F3, were showed passable flow character and F5 and F9 showed poor flow character.

Hausner's ratio

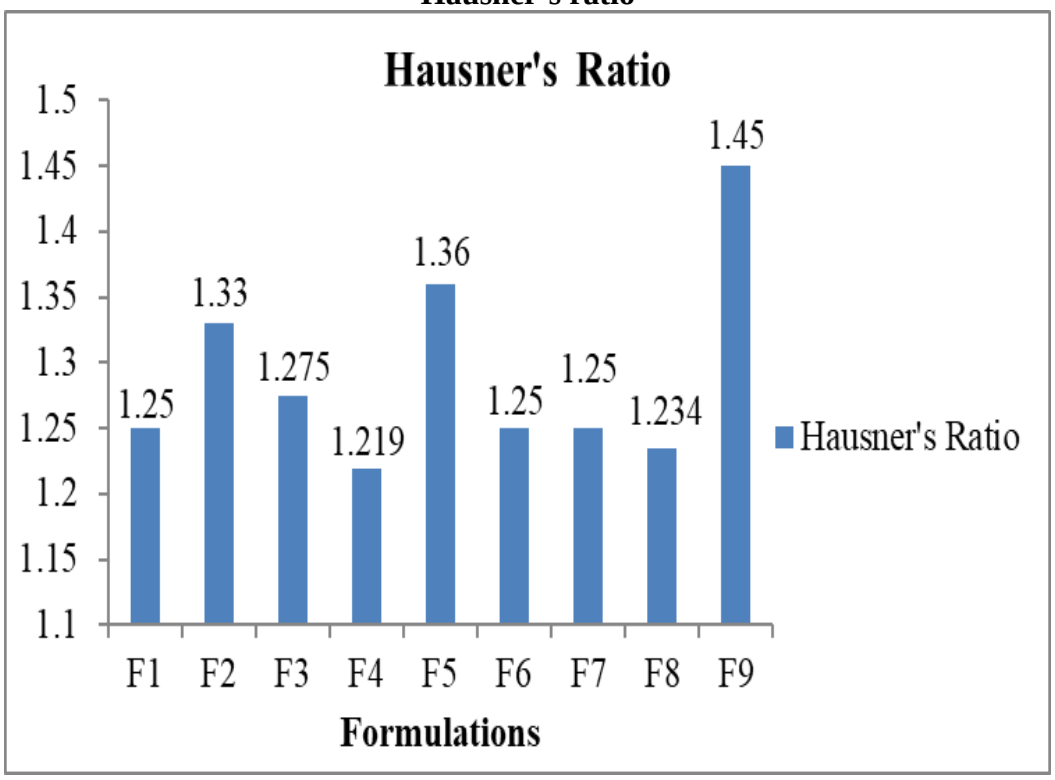


Fig 12. Bar chart for Hausner's Ratio

Since, hausner's ratio of all formulation was determined. The formulationF1, F2, F3, F4, F6, F7 and F8 showed passable flow character. The formulation F5 and F9 were showed poor flow character.

Post Compression Parameter

Thickness

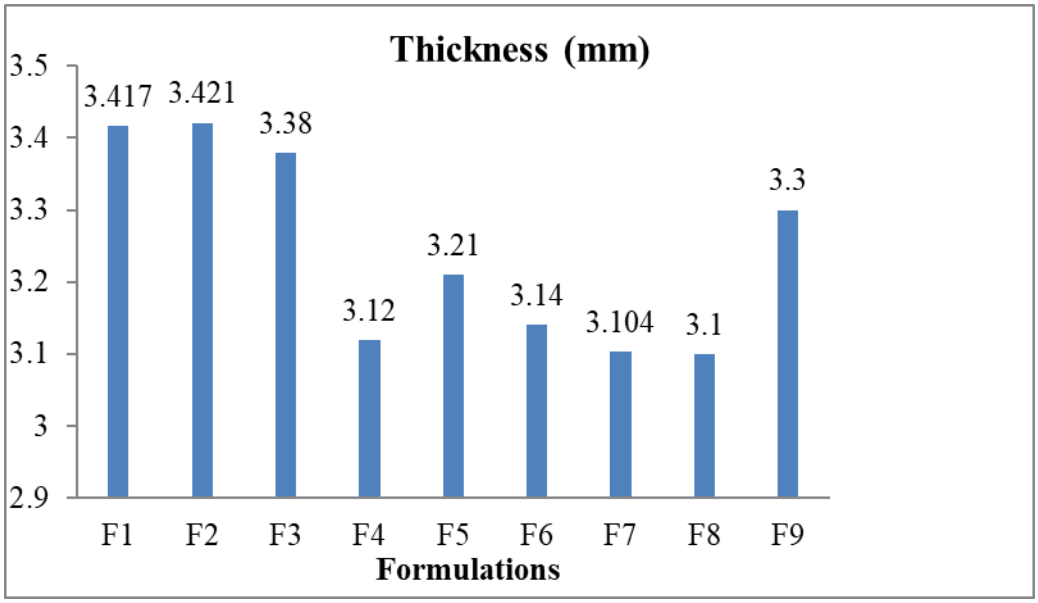


Fig. 13. Bar chart for Thickness

The thickness of all formulated tablet falls within the range of 3.1 to 3.421 mm.

Hardness

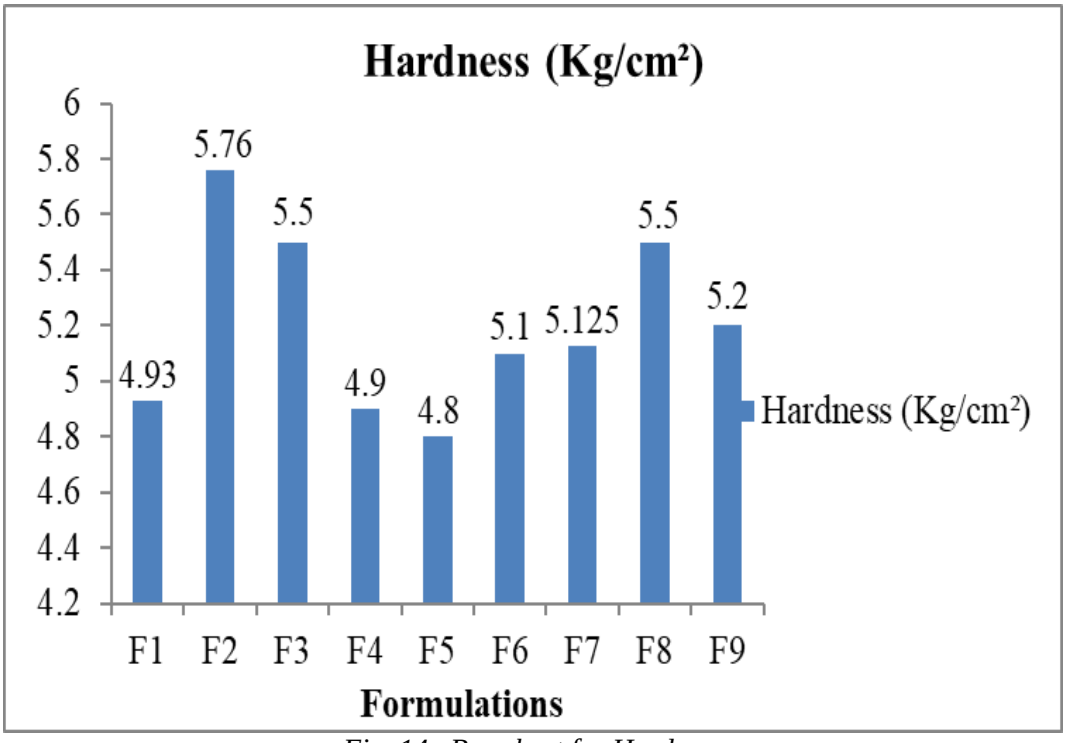


Fig. 14. Bar chart for Hardness

Hardness of tablet was found to be 4.8 to 5.76 kg/cm^2.

Friability

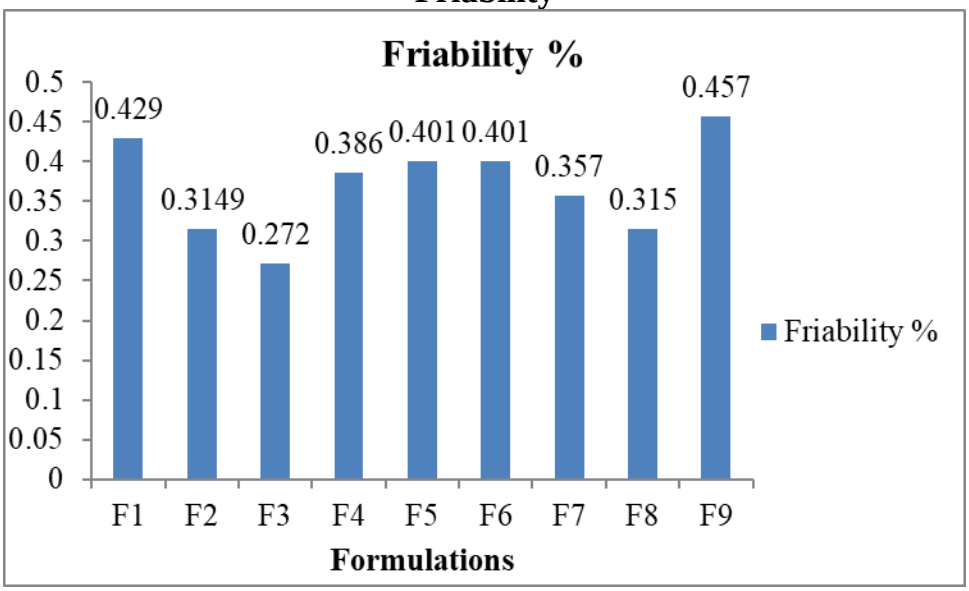


Fig. 15. Bar chart for Friability

Friability indicates the ability of tablet to withstand mechanical shocks while hand. According to IP 2010 total weight loss during the friability should be less than or equal to 1 percent (<1%). Since, all formulation were within the range thus passes the friability test. The friability range was found to be 0.272 to 0.457 %. which indicates that all formulation batches can withstand mechanical shock while handling before administration.

Dispersion Time

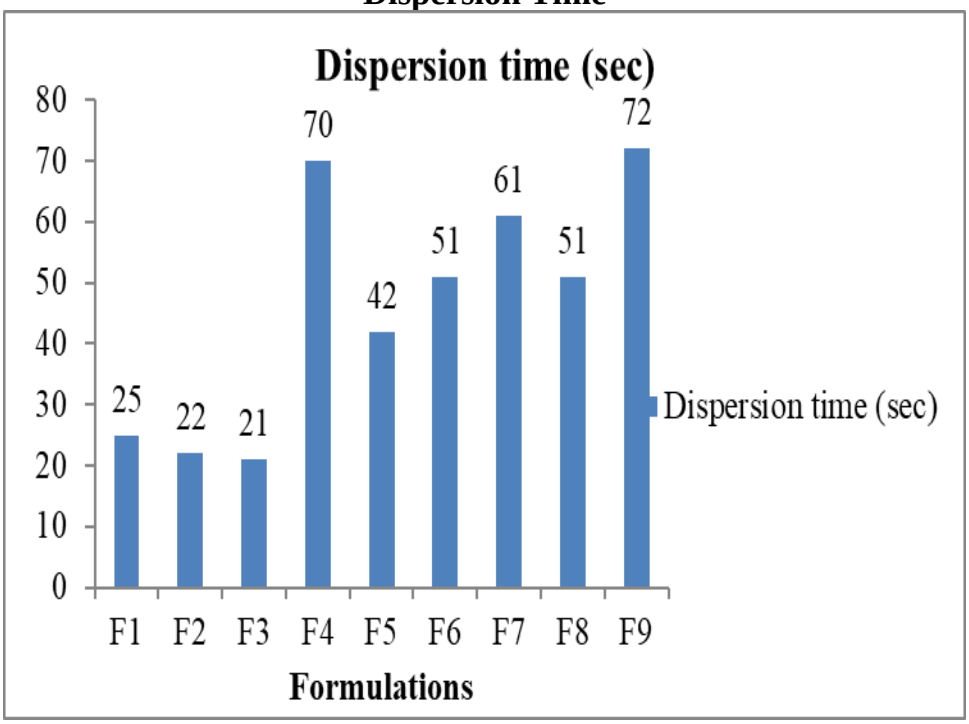


Fig. 16. Bar chart for Dispersion time

Dispersion time of all formulation were within a range *i.e.* within 3 mins (as per IP 2010) except F4, F5 and F9. Hence, the F3 showed better disintegration time than other.

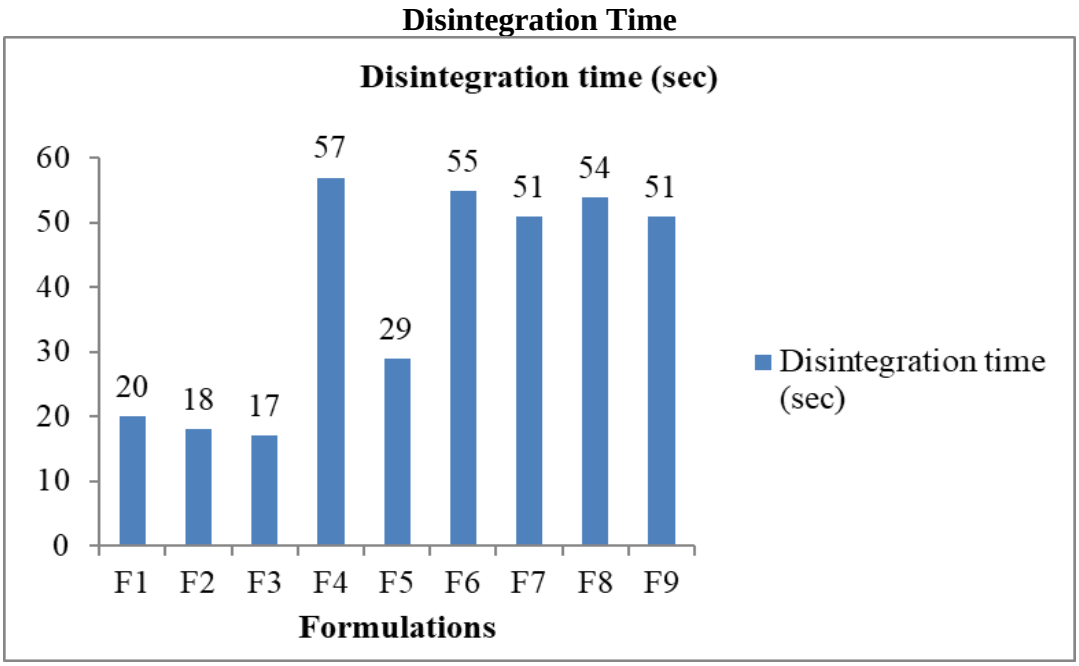


Fig 17. Bar chart for Disintegration time

Disintegration time of all formulation were within a range *i.e.* within 3 mins (as per IP 2010). Hence, all formulation passed disintegration test and the F3 showed better disintegration time than other.

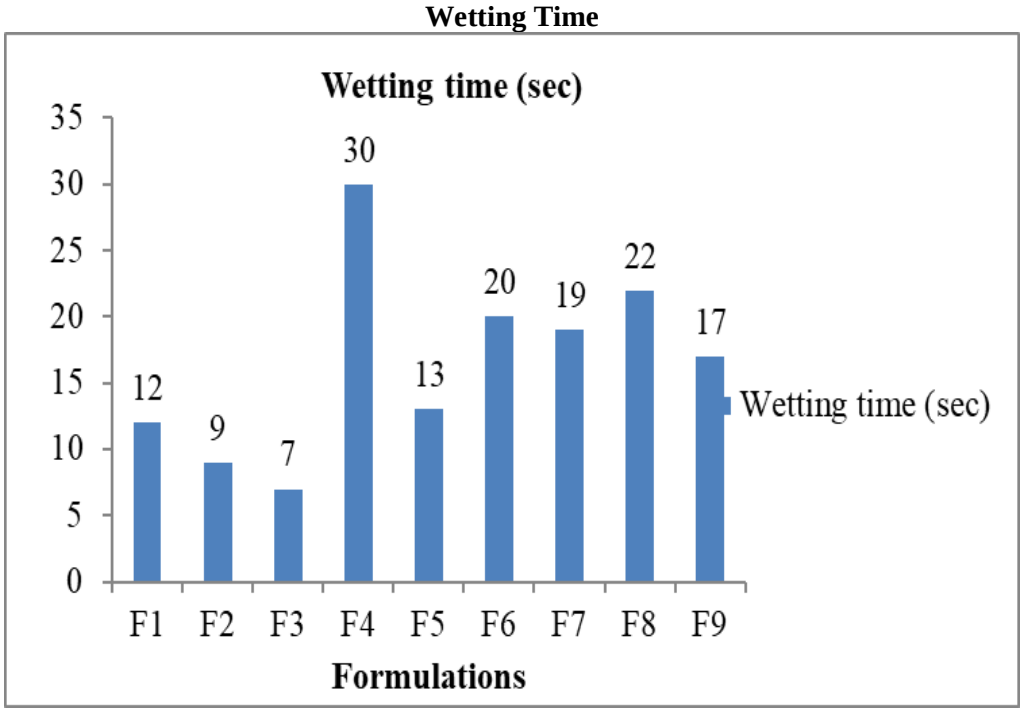


Fig 18. Bar chart for Wetting time

Among all the formulation, F3 showed best wetting time *i.e.* 7 sec.

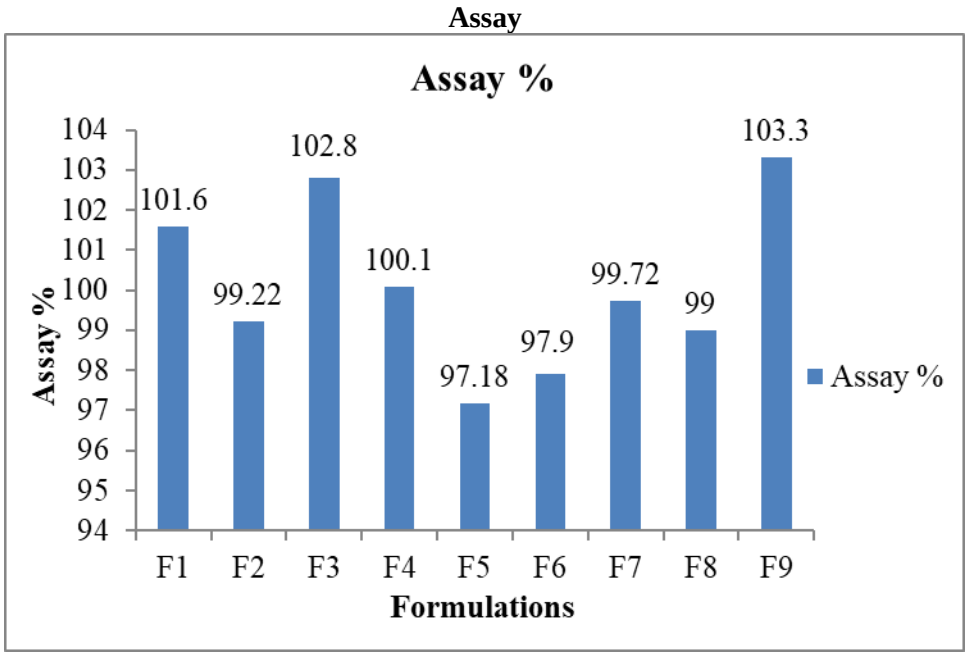


Fig 19. Bar chart for Assay

As per IP specification, the content of Etoricoxib in prepared DT of Etoricoxib should in range of NLT 95% and NMT 105%. Based on result of test all formulation were within the range.

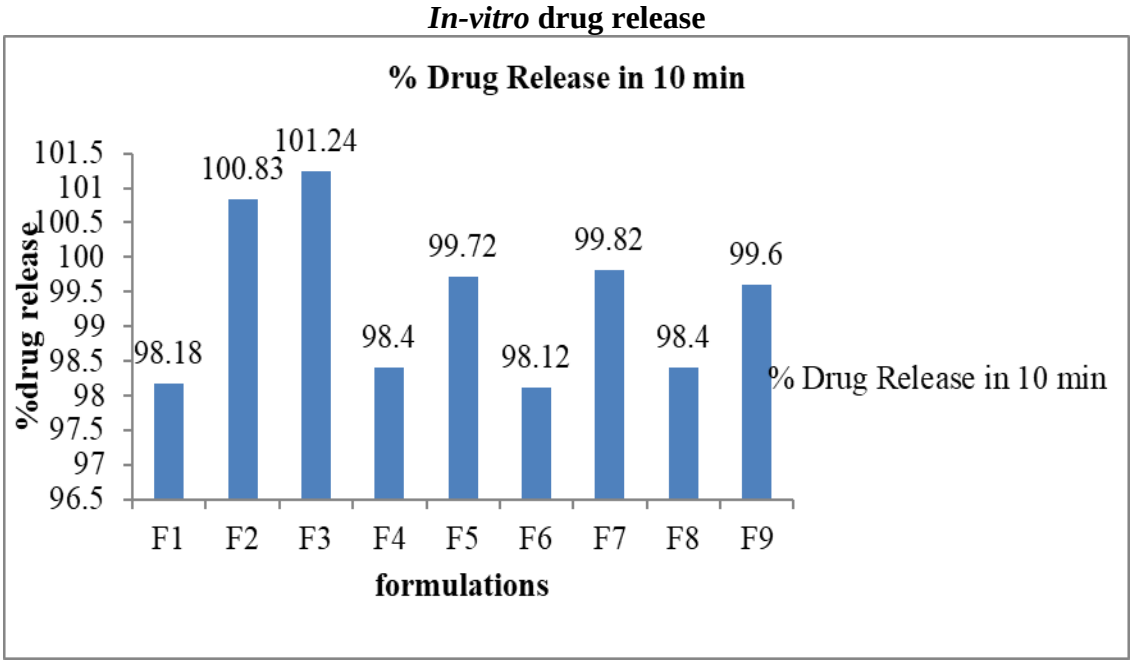


Fig 20. % Drug Release in 10 minutes for Different Formulations

CONCLUSION

Based on our laboratory, studies the following conclusions can be drawn. The mouth dissolving tablet of etoricoxib were successfully prepared by using different disintegrating agent namely crospovidone, croscarmellose sodium and sodium starch glycolate. All samples of different formulation were subjected to pre-compression and post-compression evaluations. The result indicate that F3 was the best formulation among the all formulation developed for mouth dissolving tablets. The disintegration studies shows that the tablets prepared with 9% crospovidone shows faster disintegration as compared to tablets prepared with croscarmellose sodium and sodium starch glycolate. The *in- vitro* dissolution study for tablets were carried out and tablet of formulation batch 3 containing 9% crospovidone released 101.24% of drug during 10 minutes which is fast release as compared to CCS and SSG. From the above, concluded that the fast-dissolving tablets of etoricoxib prepared with crospovidone showed better disintegration time and dissolution profile as compared to other superdisintegrants.

SUMMARY

Solid dosage form is popular because of the ease of administration, accurate dose, self-medication, pain avoidance, and most importantly the patient compliance. Tablets and capsules are the most popular solid dosage form. However, many patient groups such as the elderly, children and patient who are mentally retarded, uncooperative on reduced liquid intake/diets have difficulties swallowing these tablets and hard gelatin capsules. Thus, these conventional dosage form results in high incidence of non-compliance and ineffective therapy with respect to swallowing specially in the case of pediatric, geriatric, or any mentally retarded persons. The concept of formulating fast dissolving tablet containing etoricoxib offers suitable and practically approach in serving such patients with characteristic increases bioavailability and patient compliance. In the present work, an effort is made to formulate and evaluate fast disintegrating tablets of etoricoxib. The superdisintegrants such as Crospovidone, Croscarmelose sodium and sodium starch glycolate were used along with sweetener *i.e.* Saccharin and mannitol to impart better mouth feel in developing fast dissolving tablets. Pre-compression parameters were carried out to determine the flow properties of powder blend. Angle of repose, Bulk density, and Tapped density and also Carr's Index were determined for all the formulations, which showed good results indicating good flow properties. Post-compression parameters were conducted for the tablets. The disintegration time for all the formulations was found to be less than 17 to 55 seconds, indicating rapid disintegration. The results of the evaluation parameters demonstrate that it is possible to design and develop Fast dissolving tablets of Etoricoxib by using different superdisintegrants. Among the superdisintegrants used crospovidone showed better disintegration time and dissolution profile compared to other superdisintegrants.

REFERENCES

1) Dhirendra K, Lewis S, Udupa N, Atin K. (2009), Solid Dispersions: A Review. Pak J Pharm Sci. 22 (2): 234- 246.
2) Vasconcelos T, Sarmento B, Costa P. (2007), Solid dispersions as strategy to improve oral bioavailability of poor water soluble drugs. Drug Discov Today. 12(23/24): 1068-1075.
3) Dahiya M, Saha S, Shahiwala A. A Review on Mouth Dissolving Films. Curr Drug Deliv. 2009;6(5):469-476. doi:10.2174/156720109789941713.

4) Sahoo S, Mishra B, Biswal PK, Panda O, Mohapatra SK JG. Oral Dispersible System: A New Approach in Drug Delivery System. Molecules. 2015;20(8):14684-14698. doi:10.3390/molecules200814684
5) Bhowmik D, Chandira RM, Krishnakanth, Pankaj, B. Chiranjib. Fast Dissolving Tablet: An Overview. J Chem Pharm Res. 2009;1(1):163-177. www.jocpr.com.
6) Limited SC, Pradesh A. Oral Disintegrating Tablets – A Current Review. 2013;4(6):1134-1154.
7) Saurabh S, Rajni B, Baibhav J, Rana AC, Vikas S. Mouth Dissolving Tablets: a Futur e Compaction. Int Res J Pharm. 2012;3(8):98-109.
8) FB A, T U. Orally Disintegrating Tablets: A Short Review. J Pharm Drug Dev. 2015;3(3). doi:10.15744/2348-9782.3.303.
9) Kumar V. Dinesh, Sharma Ira, Sharma Vipin. A comprehensive review on fast dissolving tablet technology. Journal of Applied Pharmaceutical Science 2011, 01(05): 50-58.
10) Rajeshree Panigrahi SPB CSP. WebmedCentral.com:: A Review On Fast Dissolving Tablets.May 14, 2019.
11) Kumar RS, Kumar VG. Fast Dissolving Tablets: A Novel Approach To Enhance the Bioavailability of Poorly Soluble Drugs. Eur J Pharm Med Res. 2017;4(2):274-298.
12) Siddiqui N, Garg G, Sharma PK. Fast dissolving tablets: preparation, characterization and evaluation: an overview. Int J Pharm Sci Rev Res 2010;2:87-96.
13) Mishra US, Prajapati SK, Bhardwaj P. A review on formulation and evaluation for mouth dissolving tablet. World J Pharm Pharm Sci 2014;8:1778-810.
14) Nautiyal U, Singh S, Singh R, Gopal, Kakar S. Fast dissolving tablets as a novel boon: a review. J Pharm Chem Biol Sci 2014;2:5-26.
15) Pagar R, Ahirrao S, Yallatikar T, Wagh M. Review on orodispersible tablets. Int J Res Dev Pharm L Sci 2014;3:949-58
16) Sharma S. New generation of the tablet: fast dissolving tablet. Latest Rev Pharmainfo Net; 2008. p. 6.
17) Hannan PA, Khan JA, Khan A, Safiullah S. Oral dispersible system: a new approach in drug delivery syste. Indian J Pharm Sci 2016;78:2-7.
18) Mohanachandran PS, Sindhumol PG, Kiran TS. Superdisintegrants: an overview. Int J Pharm Sci Rev Res 2011;6:105-9.
19) Khan AB, Tripuraneni A. Fast dissolving tablets–a novel approach in drug delivery. Rguhs J Pharm Sci 2014;1:7-16.
20) Patel TS, Sengupta M. Fast dissolving tablet technology. World J Pharm Sci 2013;2:485-508.
21) Kuchekar BS, Badha AC, Mahajan HS. Mouth dissolving tablets: a novel drug delivery system. Pharmatimes 2003;35:7-9.
22) Kushagra Khanna, Gauravi Xavier, Suresh Kumar Joshi, Aashish Patel, Sakshum Khanna V and BG. Fast Dissolving Tablets- A Novel Approach. Int J Pharm Res Allied Sci. 2016;5(2):311-322.
23) Kaur T, Gill B, Kumar S, Gupta GD. <Mouth Dissolving Tablet Review.Pdf>. 2011;3(1):1-7.
24) DrugBank Release Version 5.1.3 - DrugBank.
25) S. S, J. K, A. A, A. C, P. J. Formulation and evaluation of mouth dissolving tablets of ranitidine HCL. Int J PharmTech Res. 2010;2(2):1574-1577.
26) Kushagra Khanna, Gauravi Xavier, Suresh Kumar Joshi, Aashish Patel, Sakshum Khanna V and BG. Fast Dissolving Tablets- A Novel Approach. Int J Pharm Res Allied Sci. 2016;5(2):311-322.

27) Bodhmage A. Correlation between physical properties and flowability indicators for fine powders. Univ Saskatchewan. 2006;(July):1-122. http://www.collectionscanada.gc.ca/obj/s4/f2/dsk3/SSU/TC-SSU-07032006115722.pdf.
28) United States Pharmacopeia. USP Powder Flow. Stage 6 Harmon. 2016;30(60)(6):7. http://www.usp.org/sites/default/files/Harmonization/Gen-Chapter/g05_pf_30_6_2004.pdf.
29) Shahi SR, Agrawal GR, Shinde N V., et al. Formulation and in vitro evaluation of oro-dispersible tablets of etoricoxib with emphasis on comparative functionality evaluation of three classes of superdisintegrants. Rasayan J Chem. 2008;1(2):292-300.
30) Indian Pharmacopeia vol II. Ghaziabad, India. India Pharmacop Comm. 2018.