Abstract

Indomethacin is class of non-steroidal anti-inflammatory drugs. It is act by inhibiting isoforms of cyclooxygenase 1 and 2. Indomethacin used in the treatment of moderate to severe rheumatoid arthritis including ankylosing spondylitis, osteoarthritis, tendinitis, bursitis and acute gouty arthritis etc. Indomethacin is practically insoluble in aqueous medium and highly permeable belong to BCS class II. Indomethacin shows very low and variable oral bioavailability due to poor dissolution in gastrointestinal fluid. This unwanted physical property of Indomethacin gives irritating side effects in gastrointestinal tract due to prolonged contact time with the mucosal layer of gastrointestinal tract. Solid dispersion methods are used to overcome this problem. Solid dispersion is commonly used technique to improve dissolution and bioavailability of poorly soluble drugs. The increase in dissolution rate for solid dispersion can be attributed to number of factors 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 development cost of any new chemical drug is very high so for that reasons research and development department of many pharmaceutical companies focusing on the development of new drug delivery system for existing active ingredients.

Novel drug delivery systems aims for designing and development of dosage forms, convenient to manufactured and administered, with reduced side effects, offering rapid release and enhanced bioavailability so as to achieve better patient compliance. In recent years, innovative drug delivery systems, like ‘Fast Dissolving Tablets’ have been developed and attracted the interest of many researchers.

Keyword: Fast Dissolving, Indomethacin, anti-inflammatory agent

1. INTRODUCTION

The effectiveness of drug is depending upon the ability of the dosage form to deliver the medicament to its site of action at a rate and amount sufficient to elicit the desired pharmacological response. This property of dosage form is referred to as physiologic availability, biologic availability or simply bioavailability. Thus the term bioavailability is defined as 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 is a scientific framework for classifying drugs substances according to 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.
Class I: (High Solubility, High Permeability)
Drugs under this class are well absorbed and their absorption rate is higher than excretion. The rate limiting step is dissolution and if drug dissolution is very rapid then gastric emptying time is rate limiting step.
Example: verapamil, Metaprolol, Diltiazem

Class II: (Low solubility, High Permeability)
The bioavailabilities of these drugs are depending upon solvation rate. Absorption rate of class II drug is slower than class I drugs.
Example: Ketocanazole, Mefenamic acid, Itraconazole

Class III: (High solubility, low permeability)
The absorption is limited by the permeation rate but the drug is solvated very fast. The drug is exhibit high variation in rate and extent of drug absorption.
Example: Cimetidine, Captopril

Class IV: (Low solubility, low permeability)
These compounds have poor bioavailability and not good to absorbed to entire gastrointestinal tract.
Example: Hydrochlorothiazide, taxol

The rate limiting step for bioavailability and absorption of active pharmaceutical ingredients are release of medicament from its dosage forms or drug permeation through the biological membrane. Drugs having high solubility and high permeability (class I), release from dosage forms occur very rapidly then gastric emptying time will be a rate limiting step for drug absorption. Whereas drugs having low solubility and high permeability (class II), release from dosage forms occur slowly. In-vivo drug dissolution is rate limiting step for absorption of class II drugs. Class II drugs exhibited variable bioavailability and need enhancement of in dissolution so as to increase drug bioavailability. There are various methods of enhancement of bioavailability.

Methods of enhancing dissolution:
- Use of surfactant
- Complexation
- By making the pro drug
- Use of selected polymeric forms
- Use of solvates and hydrates
- Use of salt of weak acids and weak bases

Methods of enhancing dissolution by increasing surface area
- Micronisation
- Solid dispersion
- Solid disposition

For class III drugs permeation through intestinal membrane is rate limiting step for drug absorption. Drugs under these class showed low bioavailability and need enhancement in permeability.
Class IV drugs exhibit variable and poor bioavailability.

BCS class boundaries:
Class boundary parameters i.e. permeability, solubility, and dissolution, are for easy identification of BCS class

1) Solubility: A drug substances is considered highly soluble when the highest dose strength is soluble in 250ml or less of water over ph range of 1-7.5 at 370c.

2) Permeability: A drug substances considered highly permeable when the extent of absorption in human is greater than 90% of administered dose depend upon massbalance or compared with intra venous reference dose.

3) Dissolution: A drug substances is considered fast dissolving when 85% or more of the labeled amount of drug substance dissolved within 30 min using USP apparatus 1 or 2 in a volume of 900 ml or less of buffer solution.
Oral route is the most common route of drug administration because of ease of ingestion and convenience in self-administration as compared to other route of administration. The oral bioavailability is depend upon various factors including aqueous solubility, permeability of drug, dissolution rate, first pass metabolism, pre-systemic metabolism. The most frequent cases of low oral bioavailability are due to poor solubility and low permeability. When an active agent is administered by oral route, initially it dissolve in gastric or intestinal fluid further there is partitioning of drug particles between fluid and membrane of GI tract and finally it enter into systemic circulation. Therefore for poorly soluble drugs (class II) dissolution is rate limiting step of drug absorption. Approximately 60 % of new drug chemical molecules and several existing drug molecules are lipophilic in nature and low aqueous solubility. [1,5].

1.1 Solid Dispersion

The concept of solid dispersion was proposed by Sekiguchi and Obi in 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 in the dosage forms.

1.2. Classification of solid dispersion:

a) Simple eutectic mixture
b) Solid solution
c) Glass solution
d) Amorphous precipitation in crystalline carrier
e) Complex formation

a. Simple eutectic mixture:
A simple eutectic mixture is an intimately blended physical mixture of two crystalline components, which are miscible in the liquid state, but immiscible in solid state. A mixture of components A and B with composition E is cooled then A and B crystallize out simultaneously. Whereas when other composition is cooled, one of the components starts to crystallize out before the other.

b. Solid solution:
Solid solution consists of a solid solute particles dissolved in a solid solvent. The particle size is reduced up to molecular level. When the drug is dispersed in the carrier matrix, its effective surface area is significantly higher and hence the dissolution rate is enhanced. Solid solution has improved physical stability of amorphous drug by inhibiting drug crystallization by reducing molecular mobility. Solid solution is classified into sub types are as follow: Depending upon their miscibility characteristics –

i. Continuous solid solution
ii. Discontinuous solid solution

Depending upon by the in which solute/solvent molecules are distributed in the lattice

i. Interstitial solid solution
ii. Substitutional or amorphous solid solution

i. Continuous solid solution:
In a continuous solid solution, the components are miscible with another in all proportion in both liquid and solid state. The lattice energy of the continuous solid solution at all compositions is higher than that of the respective pure components in the solid state, because the heteromolecular bonding strength is higher than the homomolecular one in order to form a continuous solid solution.
ii. Discontinuous solid solution:
In this class, the miscibility or solubility of one component in the other is limited. The region $\alpha$ is a solid solution of B in A that is component A as the solvent and B as the solute. Similarly the region $\beta$ is a solid solution of A in B. Beneath a certain temperature, the common solubility of the two constituents start to decline.

iii. Interstitial solid solution:
In interstitial solid solutions the dissolved drug molecules occupy the interstitial spaces between the solvent molecules in the solvent crystal lattice.

iv. Substitutional solid solution:
In the substitutional solid solution the solute molecule are dispersed molecularly but irregularly within an amorphous solvent lattice.

c. Glass solution:
Glass solution is an amorphous, homogeneous solution method in which a glossy or a clear form of the carrier solubilises drug molecules. The glassy or vitreous state characterizes by transparency and brittleness below the glass transition temperature ($T_g$). The advantage of glass solution over the solid solution is that they do not possess a strong lattice like a solid solution so that they do not present this barrier to rapid dissolution. The main disadvantages of glass solution is that the glassy state is metastable as compared to crystalline state, and depending upon its physicochemical properties and storage conditions a glass can convert into a crystalline soli.

d. Amorphous precipitation in a crystalline carrier:
Instead of simultaneous crystallization of the drug and the carrier, the drug may also precipitate in an amorphous form in the crystalline forms of the drug.

e. Complex formation:
In the complex formation, a drug forms a complex with water soluble carrier in the solid state. The availability of drug is depend on the stability constant of the complex, solubility and the absorption rate of the drug. Due to formation of water soluble complex, dissolution rate and oral absorption of drug is enhanced. Example – cyclodextrin [8]

1.3. Carriers used in the solid dispersion:
Carriers are the substances which are soluble and dissolve in water at a fast rate, are widely used in pharmaceutical formulations to enhance dissolution of drugs.

a. Polyethylene Glycol:
Range of 200 – 300000. Their water solubility is good but generally deceases with increasing molecular weight. They have good solubility in organic solvents. The melting point of PEGs are lies under 650c. These relatively low melting points are advantageous for the preparation of solid dispersion by melting method.

b. Poly vinyl pyrrolidone:
Polymerization of vinyl pyrrolidone forms poly vinyl pyrrolidone (PVP) of molecular weight ranging 2500 – 3000000. They can be classified according to the K value. They have good water solubility and in organic solvents.
Therefore, They are particularly suitable for preparation of solid dispersion by solvent evaporation method. The chainlength of PVP greatly influence on dissolution rate of drug dispersed in a solid dispersion. The water solubility and viscosity of PVP becomes lower with increasing chain length.

c. Urea
Urea is the end product of human protein metabolism, has diuretic effect and non toxic. Its solubility in water is greater than 1 in 1 and it also exhibit good solubility in many organic solvents. Urea is not often used as carrier now days.

d. Sugars:
Sugars and related compounds are highly water soluble. The melting point of many sugars is high, so that making solid dispersions by melting method is problematic. Solubility of sugars in organic solvents is poor. Due to these drawbacks they are less suitable carrier than other carriers for the manufacturing of solid dispersion. Despite these limitations several attempts to prepare solid dispersion by using sugars like lactose, mannitol, chitosan, sorbitol etc.

e. Cellulose derivatives:
Cellulose is naturally occurring polysaccharides. They consists of high molecular weight unbranched chains, in which the saccharides units are linked together by β-1, 4-glycoside bonds. The cellulose can be derivatized to form methyl cellulose, hydroxypropyl cellulose, and other semi synthetic cellulose by appropriate alkylation.

f. Eudragits (Polyacrylates and polymethacrylates):
Polyacrylates and polymethacrylates are glossy materials that are formed by the polymerization of acrylic and methacrylic acid and byproducts of these polymers such as esters amides and nitriles. Commonly they are referred by trade name Eudragit. Among all the Eudragits, Eudragit E is used to improve release rate of poorly soluble drugs

g. Emulsifiers:
By improving wetting characteristics and solubilisation of drug, emulsifying agents can be used as carriers. Due to potential toxicity problems emulsifying agents are used in combination with another carrier. Examples – tween 20, polysorbate 80, Myrj 52, pluronic F 98, Gelucire® 44/14

1.4. Method of preparation of solid dispersion:
Various preparation methods of solid dispersions are as follows

a. Fusion method:
The fusion method also called as the melt method. In this method, the melting phase is consists of suspended active drug in a previously melted carrier mass, instead of using both drug and carrier in the melted state, therefore reducing the process time and temperature. After cooling, the obtained mixture must be pulverized regarding further use. This method is less difficult technically. However, the use of high temperature, several drugs can be degraded during melting process can be a limitation of this method. Another limitation of method is incomplete miscibility of drug and carrier. To avoid this limitation several modification were introduced to the original method like hot stageext rusion method, melt agglomeration method.

b. Solvent method:
This method consists of two main steps; first step consists of preparation of solution containing carrier material and drug. Another step involves the removal of solvents resulting in formation of a solid dispersion. Due to mixing at molecular level, dissolution properties of poorly soluble drugs are increases. Common advantages of this method are – 1) Preparation of solid dispersion of thermo labile substances is possible with this solvent method. 2) Also polymers that could not be used for melting method due to their high melting points could be now considered as carrier possibilities Identification of common solvents for both carrier and drug can be problematic. Complete removal of solvent from the prepared product can be lengthy process. Also large volume of solvent are required which can leads to toxicological problems.

c. Hot melt extrusion:
This method consists of the extrusion, at high rotational speed, of the carrier and drug, previously mixed, at melting temperature for little period of time. The obtained product is collected after cooling and then milled.
Hot melt extrusion method offers several advantages over traditional techniques including the absence of solvents, limited processing steps, continuous operation and improved bioavailability.

d. Supercritical Fluid (SCF) process:
Supercritical fluid (SCF) is a novel nanosizing and solubilization technology. Supercritical fluid are fluids whose pressure and temperature are greater than its critical pressure (TP) and critical temperature (TC), allowing it to assume the properties of gas and liquid. When the drug atoms are solubilised in SCF, they can be recrystallised at importantly decrease particle sizes. This method is eco-friendly, safe and economical.

e. Lyophilization method:
In this lyophilization technique, drug and carrier are dissolved in a common solvent, frozen and sublimed to obtain a lyophilized molecular dispersion. This method was proposed as an alternative method to solvent evaporation.

f. Spray drying:
In this method, suspensions or solutions is atomizing into fine droplets followed by a drying process which gives fine dust free powder as well as agglomerated one to precise specifications. Spray drying is simple and cost effective method. Now days, spray drying finds great application in pharmaceutical industry because of fast drying and specific characteristics like particle size and shape of the final product. [9]

1.5. Advantages of solid dispersions:
There are several reasons for the improvement of solubility of poorly water soluble drug by using solid dispersion methods. The advantages of solid dispersion or the reasons for solid dispersions are as follows:

Particles with reduced particle size:
In the solid dispersions, drug is dissolved in dissolution medium or inert matrix. A high surface area is formed which gives increased dissolution rate and further enhance the bioavailability of poorly water soluble drug.

Particle with improved wettability:
Solid dispersions improved the wettability of poorly water soluble drug due to this improved in bioavailability of drug.

Particle with higher porosity:
Particles in solid dispersion have found to have high porosity. Porous nature of particle results higher dissolution rate. Increase in porosity of particles is depend upon properties of carrier .when the polymer having linear structure are utilized it formed larger and porous particles compared with solid dispersion that prepared with reticular polymer.

Drug in amorphous state:
Drug substances in amorphous state shows higher drug release because no energy is required to break up the crystal lattice during dissolution. Therefore, poorly water soluble drug in amorphous state gives high degree of solubility.

1.6. Disadvantages of solid dispersion:
Instability is the major disadvantage of solid dispersion. Many solid dispersion systems have shown changes in crystallinity on ageing, phase separation, by moisture absorption, crystal growth which leads to decrease in dissolution rate and reduction of drug solubility. Presence of moisture and temperature enhance the deteriorating effect on solid dispersion. Many times it is difficult to handle because of tackiness.

1.7. Limitations of solid dispersions:
Although a great interest in solid dispersion in the past few decades, the commercial application is very limited .problems or limitations of solid dispersion involve-

- The chemical and physical stability of drugs and vehicles
- Method of preparation of solid dispersion
- Reproducibility of its various physicochemical characteristics
- Formulation of solid dispersion into various dosage forms
- Scale up of manufacturing processes[10]

1.8. Pharmaceutical applications of solid dispersions:
Apart from solubility enhancement, the solid dispersion method may have number of pharmaceutical applications, which should be further explored.

➢ To obtain a homogeneous distribution of very small amount of drug substances in solid state
➢ To dispense various liquid or gaseous compounds in solid dosage forms
➢ To stabilize various unstable drugs
➢ To formulate immediate release primary dose in sustained release dosage forms
➢ To formulate sustained release regimen of soluble drug by using various insoluble or poorly soluble polymers or carriers.
➢ To reduce first pass metabolism or pre systemic inactivation of various drugs like morphine, progesterone.[11]

1.9. Fast Dissolving Tablet:

1.9.1. Definition

United States Food and Drug Administration (USFDA) defined fast dissolving tablet as “A solid dosage forms containing active ingredient or medical substances which disintegrates rapidly within a matter of seconds when placed upon the tongue.” The disintegration time for fast dissolving tablets ranges from few seconds to about a minute.

Also, United state Pharmacopeia approved this dosage form as orally disintegrating tablet. European pharmacopeia defines a similar terms, 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 as 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 are also appreciated by pediatric, geriatric patients, institutional patients along with mentally disabled patients who enable to take self-medication, and patients who suffering from nausea, vomiting and motion sickness complications. Fast dissolving tablets are also 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 a good mouth feeling and tastes, leaving minimal residue in 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. [12]

1.9.2 Requirements of fast dissolving tablet

➢ It should have pleasant mouth feel
➢ It should have Acceptable taste masking property
➢ Require no water for oral administration
➢ Be harder and less friable
➢ Less sensitive to environmental condition
➢ Allow high dose medicines

1.9.3 Salient feature of fast dissolving tablet

➢ Fast dissolving tablets does not require water for oral administration
➢ Fast dissolving tablets having sufficient hardness to withstand the rigor of the manufacturing process and handing during transportation.
➢ Allow high drug loading
➢ It should have pleasant mouth feel
➢ Cost effective

1.9.4 Advantages of fast dissolving tablets:

➢ Fast dissolving tablets is beneficial for the patients who cannot swallow, like elderly, bedridden stroke victims, patients suffering from renal failure and psychiatric patients.
➢ Rapid drug delivery intervention
➢ Convenient for administration
➢ Enhances bioavailability of poorly water soluble drugs through pre-gastric absorption of drug from mouth, esophagus as saliva passes down.
➢ Good mouth feel property which enhances patients acceptability
➢ The choking or suffocation during oral administration of conventional dosage forms is avoided.
➢ New business opportunity like product differentiation, promotion of product, patent extension and life cycle management.

1.9.5 Limitation of fast dissolving tablets:
Careful handling is required due to insufficient mechanical strength.

The tablets may leave grittiness in mouth if not formulated properly.[13]

1.9.6 Disadvantages of fast dissolving tablets:

- It is hygroscopic in nature so must be store in dry places
- Fast dissolving tablets also shows the fragile, effervesces granules property.
- It require special packing for stabilization of product [14]

1.9.7 Conventional method of preparation of fast dissolving tablets:

a) Lyophilization:
This method is also called as freeze drying method. The fast dissolving tablets prepared by lyophilization method are porous in nature so as to dissolve or disintegrate in saliva very easily. First step is material is frozen below its eutectic point which follow the primary drying to reduce the moisture to around 4% w/w of dry product. Finally secondary drying is done to reduce the bound moisture up to the required volume.

b) Spray drying:
This method gives highly porous tablets. Tablet is compressed from spray dried powder obtained from spray drying which disintegrated within 20seconds when come in contact with saliva. The formulation contains hydrolyzed or non-hydrolyzed gelatins as a supporting agent, sodium starch glycolate as a super disintegrate, and acidic material like citric acid and alkali material.

c) Sublimation:
The formulation consists of solid ingredients like ammonium carbonate, camphor that volatilize readily. These materials were removed via sublimation process which gives porous structure .Some solvents like benzene can also use as pore forming agents.

d) Direct compression method
This method is simple and cost effective .This method is commonly used method for manufacturing of fast dissolving tablets because of availability of improved excipients like superdisintegrates and sugar based excipients.

e) Superdisintegrants:
Superdisintegrants mainly affect the rate of disintegration and the dissolution .sodium starch glycolate, croscarmelllose sodium, crospovidone are some examples of commonly used superdisintegrants.

f) Sugar based excipients:
The sugar based exipients especially bulking agents like maltose starch dextrose fructose which are highly soluble in aqueous media and sweetness, and impart taste masking properties.

g) Mass extrusion method:
This method involves softening the active blend using solvent (mixture of methanol and polyethylene glycol) and subsequent expulsion through extruder or syringe to obtain cylinder of product which further cut into even segments by using heated blade.

h) Cotton candy process:
This method utilizes high spinning mechanism to provide floss like crystalline structure which mimics spun sugar. This technique includes creation of matrix of polysaccharides by synchronized process of flash melting or spinning. This matrix is partially recrystalised result in improved flow properties or compressibility. Further obtained matrix is milled in appropriate size and blended with active ingredient and other excipients and subsequently compressed to fast dissolving tablets.

i) Tablet molding method:
This method is of two types i.e. heat method and solvent method .In the solvent method, powder blend is moistens with hydro alcoholic solvents followed by compression at depression in molded plates. The solvent is removed by drying. within the heat molding method, preparation of suspension that contains drug agar and sugar then pouring the suspension into blister packaging wells, solidifying agar at too temperature to create a jelly and drying under vacuum

1.9.9 Mechanism of action of disintegrants:
There are various mechanisms of action of disintegrants as follows:

a) By capillary action:
Once we put the tablet into a suitable aqueous medium, the medium penetrates into the tablet and replaces the air adsorbed on the particles, which declines the intermolecular bond and breaks the tablet into well-particles. For these styles of disintegrants, maintenance of porous structure and low interfacial surface tension towards aqueous fluid is critical which helps in disintegration by creating a hydrophilic network around the drug particles.

b) By swelling:
Tablets with high porosity show poor disintegration because of lack of adequate swelling force. On the opposite hand, sufficient swelling force is exerted within the tablet with low porosity. It’s worthwhile to notice that if the packing fraction is incredibly high, fluid is unable to penetrate within the tablet and disintegration is again slows down.

c) Because of heat of wetting (air expansion):
When disintegrants with exothermic properties get wetted, localized stress is generated thanks to capillary expansion, which helps in disintegration of tablets.

d) Due to release of gases:
CO2 released within tablets on wetting thanks to interaction between bicarbonate and carbonate with acid or hydroxy acid. The tablet disintegrates thanks to generation of pressure within the tablet. This effervescent mixture is employed when pharmacist must formulate very rapidly dissolving tablets or fast disintegrating tablets.

e) By enzymatic reaction:
Here, enzymes present within the body act as disintegrants. These enzymes destroy the binding action of binder and helps in disintegration. Actually, thanks to swelling, pressure exerted within the outer direction or radial direction, it causes tablet to burst or the accelerated absorption of water resulting in an infinite increase within the volume of granules to market disintegration.

f) Due to disintegrating particle/particle repulsive forces:
Guyot-Hermann has proposed a particle repulsion theory supported the observation that non-swelling particle also because of disintegration of tablets. The electrical repulsive forces mid atoms are the mechanism of disintegration and H2O is required for it. Researchers found that repulsion is secondary to wicking.

g) Due to deformation:
Hess had proved that in tablet compression, disintegrated particles get deformed and these deformed particles get into their normal structure after they are available in contact with aqueous media or water. The swelling capacity of starch was improved when particles were extensively deformed during compression. This rise in size of the deformed atoms produces a breakup of the tablet. This could be a mechanism of starch.
2. DRUG PROFILE

2.1 Chemical data of Indomethacin[33-36]

Name: Indomethacin

Chemical name: 2-{1-[(4-chlorophenyl) carbonyl]-5-methoxy-2-methyl-1H-indol-3-yl} acetic acid

Description:
Indomethacin is a non-steroidal anti-inflammatory agent (NSAIA) with anti-inflammatory, analgesic and antipyretic activity. Its pharmacological activity is thought to be mediated through inhibition of the enzyme cyclooxygenase (COX), the enzyme responsible for catalyzes the rate-limiting step in prostaglandin synthesis via the arachidonic acid pathway.

Molecular weight: 357.788

Melting point: 158 -1620c

Molecular formula: C19H16ClNO4

Structural formula:

![Fig. No.7: Structure of Indomethacin](image)

Chemical (IUPAC) name: 2-{1-[(4-chlorophenyl) carbonyl]-5-methoxy-2-methyl-1H-indol-3-yl} acetic acid

pKa: 4.5

Solubility: Practically insoluble in water, soluble in 1in 50 of alcohol, 1 in 30 of chloroform, 1 in 40 of ether

2.2 Pharmacological data:

2.2.1 Mechanism of action:

Indomethacin may be a cyclooxygenase (COX or prostaglandin G/H synthase) inhibitor that act on both COX-1 and COX-2. Cyclooxygenase catalyzes the conversion of arachidonic acid to variety of prostaglandins involved in pain, fever, inflammation and swelling. Indomethacin antagonizes COX by binding to the upper portion of site. Indomethacin is more selective for COX-1 than COX-2, which provides more adverse gastric effects than other NSAI.D.COX-1 is required for maintaining protective gastric mucosal layer. Antipyretic effect of Indomethacin occurs as a results of increasing peripheral blood flow, vasodilation and warmth dissipation. The analgesic and anti inflammatory effects of Indomethacin occur as a results of decreased prostaglandin synthesis.

2.2.2 Pharmacokinetics:

Indomethacin is well absorbed orally. Plasma t1/2 is 2-5 hours. It’s 90 stationary to plasma proteins. It’s partly metabolized in liver and excreted by kidney.

2.2.3 Therapeutic uses:

Indomethacin, an indole acetic acid derivative, is a NASID. It is used in musculoskeletal and joint disorders including ankylosing spondylitis, osteoarthritis, rheumatoid arthritis, and acute gout, and in particular disorders such as bursitis and tendinitis. It may also be used in inflammation, pain, and oedema following orthopedic procedures, in mild to moderate pain in conditions such as dysmenorrhea, and it has used in management of postoperative pain as an adjunct to opioids and in the treatment of fever.
### 2.2.4 Side effects:

Gastrointestinal disturbances, headache, vertigo, dizziness and lightheadedness. Gastrointestinal perforation, ulceration, and bleeding may also be occurring. Hypersensitive reactions may also occur in aspirin sensitive patients. Rectal irritation and bleeding has been reported occasionally in case of indomethacin suppositories.

### 2.3 Dosage and administration:

- Standard Oral dose: 25mg/50mg/75mg
- Capsule Oral (25mg/50mg) and extended release (75 mg)
- Injection Intravenous 1 mg
- Suppository Rectal 100mg

### 3. BIBLIOGRAPHY

[1] Khodaverdi E et al., (2012) formulated a solid dispersion of Indomethacin using PVP K30 and somalt in weight ratio of 2%, 10% and 30% by using solvent evaporation technique and hot melt method. Solid dispersion was characterized by X-ray powder diffraction, Differential Scanning Colorimetry and dissolution test.

[2] K Chauhan, R Solanki, S Sharma - Int J App Pharm,(2018 )- innovareacademics.org In the present scientific scenario, the drug delivery technology has become extremely competitive and quickly evolving with ever-increasing demand. Fast dissolving tablet (FDT) is one such style of an innovative and distinctive drug delivery system.

[3] A Masih, A Kumar, S Singh... - Int J Curr Pharm (2017 )- pdfs.semanticscholar.org Fast dissolving Tablets emerge as one of the popular and widely accepted dosage forms, especially for pediatric patients because of incomplete development of the muscular and nervous system.

[4] Drug Delivery and Disposition, KU Leuven, Leuven, Belgium(2016) Spray drying is a well-established manufacturing technique which can be used to formulate amorphous solid dispersions (ASDs) which is an effective strategy to deliver poorly water soluble drugs (PWSDs).


