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"Review On Biopharmaceutical Classification System Of Metoprolol And Aceclofenac"

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ABSTRACT

The Biopharmaceutical Classification System (BCS) was created to minimise the need for in vivo bioequivalence studies and to enable in vitro dissolution experiments to be used as a proxy for in vivo bioequivalence studies. The biopharmaceutical classification system classifies pharmacological compounds based on their solubility ratio, dissolution, and intestinal permeability. It enables drug products' in vivo pharmacokinetic performance to be predicted. The BCS categorization system's concepts may be used to NDA and ANDA approvals, as well as scale-up and post-approval drug manufacturing adjustments. As a result, pharmaceutical businesses may save a substantial amount of time and money on product development. The drug can be classified into four classes of the BCS namely, high solubility high permeability, low solubility high permeability, high solubility low permeability, low solubility low permeability. The formulation scientist can use BCS knowledge to produce appropriate dose forms based on mechanistic rather than empirical methodologies. Solubility- and dissolution-enhancing formulation strategies based on the supersaturation principle to enhance the extent of drug absorption, along with the applications of the BDDCS to the understanding of disposition phenomena are reviewed. Finally, recent classification systems relevant either to the BCS or the BDDCS are presented.

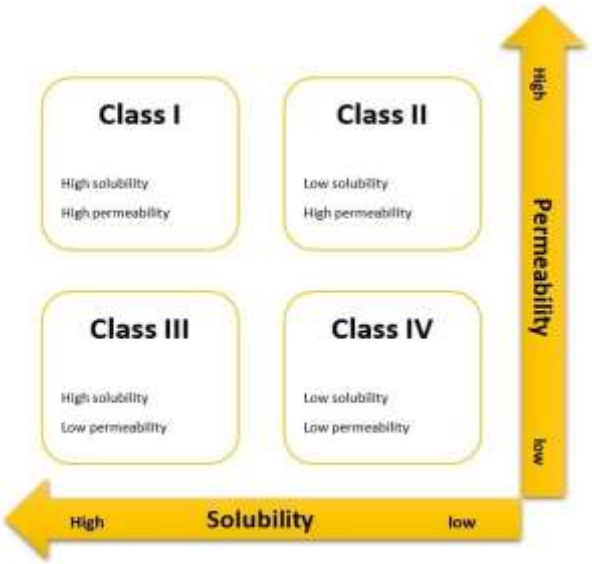
INTRODUCTION

- **Background and Objective**

Two drug products containing the same drug substance(s) are considered bioequivalent if their bioavailabilities (rate and extent of drug absorption) after administration in the same molar dose lie within acceptable predefined limits. These limits are set to ensure comparable in vivo performance, i.e., similarity in terms of safety and efficacy. In in vivo bioequivalence studies, the pivotal pharmacokinetic parameters AUC (area under the concentration time curve) and Cmax (maximum concentration), are generally used to assess the rate and extent of drug absorption.

- The BCS (Biopharmaceutics Classification System)-based biowaiver approach is intended to reduce the need for in vivo bioequivalence studies i.e., it can provide a surrogate for in vivo bioequivalence. In vivo bioequivalence studies may be exempted if an assumption of equivalence in in vivo performance can be justified by satisfactory in vitro data. The BCS is a scientific approach based on the aqueous solubility and intestinal permeability characteristics of the drug substance(s). The BCS categorizes drug substances into one of four BCS classes as follows:

  Class I: high solubility, high permeability Class II: low solubility, high permeability Class III: high solubility, low permeability Class IV: low solubility, low permeability



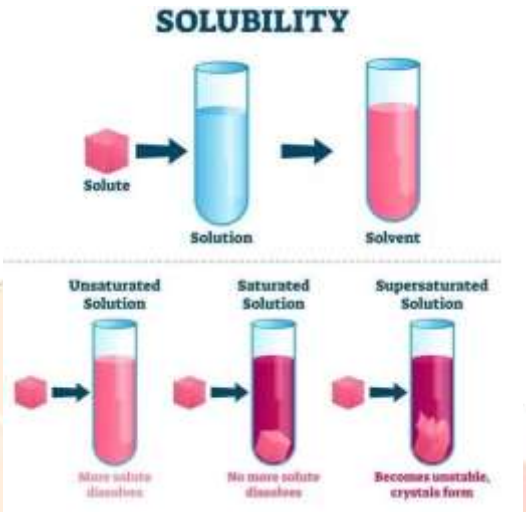
"BIOPHARMACEUTICAL CLASSIFICATION SYSTEM"

❖ **SOLUBILITY**

- A drug substance is classified as highly soluble if the highest single therapeutic dose is completely soluble in 250 ml or less of aqueous media over the pH range of 1.2–6.8 at 37±1°C. In cases where the highest single therapeutic dose does not meet this criterion but the highest strength of the reference product is soluble under the aforementioned conditions, additional data should be submitted to justify the BCS-based biowaiver approach.
- The sponsor is expected to establish experimentally the solubility of the drug substance over the pH range of 1.2–6.8 at 37±1ºC. At least three pHs within this range, including buffers at pH 1.2, 4.5 and 6.8, should be evaluated. In addition, solubility at the pH of lowest solubility of the drug substance should be evaluated if it is within the specified pH range. These experiments should demonstrate that solubility is maintained over relevant timeframes to accommodate the expected duration of absorption.
- Solubility should be evaluated by a method appropriate to the properties of the drug substance.
- Equilibrium solubility experiments may be performed, using a shake-flask technique or an alternative method, if justified. Small volumes of solubility media may be employed if the available experimental

apparatus will permit it. The pH for each test solution should be measured after the addition of the drug substance and at the end of the equilibrium solubility study to ensure the solubility measurement is conducted under the specified pH. The pH should be adjusted if necessary. The experiment should be conducted over a suitable timeframe to reach equilibrium.

- Alternatively, solubility experiments where the highest therapeutic single dose is examined in a 250 ml volume, or a proportionally smaller amount examined in a proportionally smaller volume of buffer, can be considered. The lowest measured solubility over the pH range of 1.2–6.8 will be used to classify the drug substance.

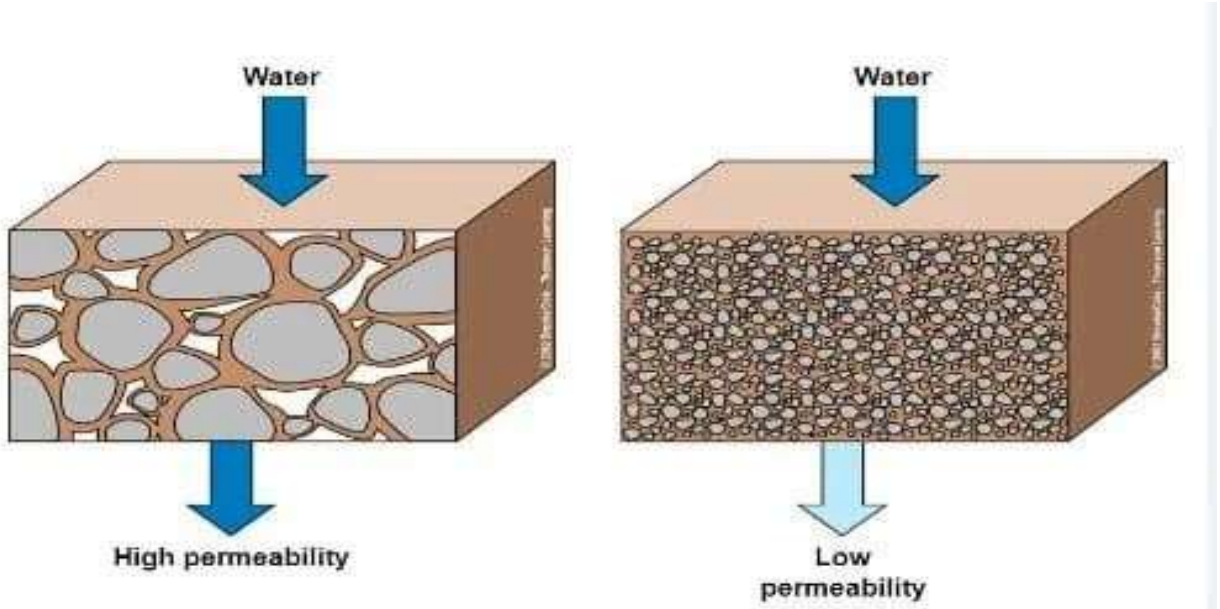


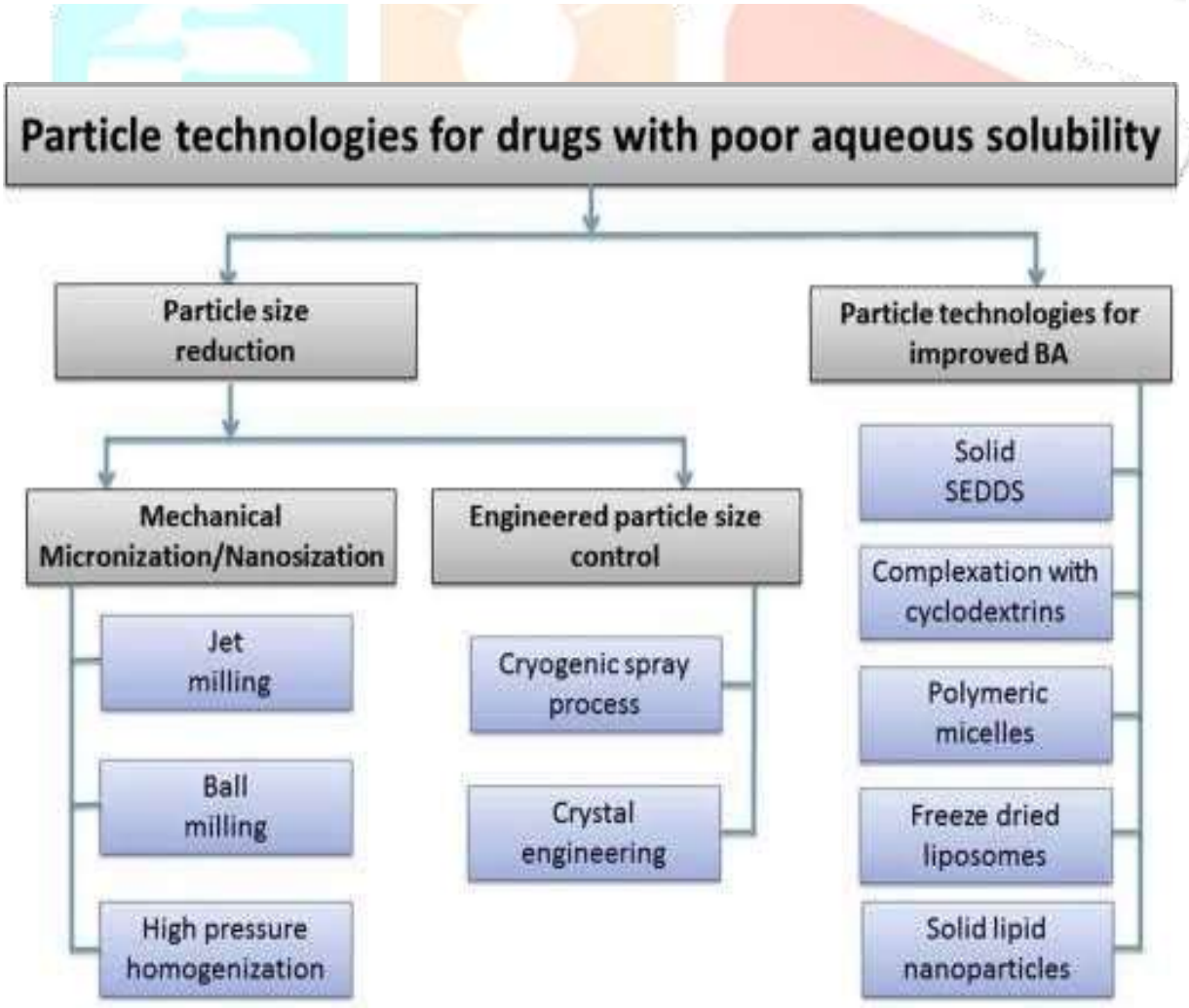
❖ PERMEABILITY

- The assessment of permeability should preferentially be based on the extent of absorption derived from human pharmacokinetic studies, e.g., absolute bioavailability or mass balance
- High permeability can be concluded when the absolute bioavailability is ≥85%. High permeability can also be concluded if ≥85% of the administered dose is recovered in urine as unchanged (parent drug), or as the sum of parent drug, Phase 1 oxidative and Phase 2 conjugative metabolites. Regarding metabolites in feces, only oxidative and conjugative metabolites can be considered. Metabolites produced through reduction or hydrolysis should not be included, unless it can be demonstrated that they are not produced prior to absorption, e.g., by microbial action within the gastrointestinal tract. Unchanged drug in feces cannot be counted toward the extent of absorption, unless appropriate data supports that the amount of parent drug in feces to be accounted for absorbed drug material is from biliary excretion, intestinal secretion or originates from an unstable metabolite, e.g., glucuronide, sulphate, N-oxide, that has been converted back to the parent by the action of microbial organisms.
- Human in vivo data derived from published literature (e.g., product knowledge and bioavailability studies) may be acceptable, keeping in mind that peer reviewed articles may not contain the necessary details of the testing to make a judgement regarding the quality of the results.
- Permeability can be also assessed by validated and standardized in vitro methods using Caco-2 cells (see Annex I). The results from Caco-2 permeability assays should be discussed in the context of available data on human pharmacokinetics. If high permeability is inferred by means of an in vitro cell system, permeability

independent of active transport should be proven as outlined in Annex I, "Caco-2 cell permeability assay method considerations".

- If high permeability is not demonstrated, the drug substance is considered to have low permeability for BCS classification purposes.





"PHARMACEUTICAL PARCTICLE TECHNOLOGIES FOR IMPROVED SOLUBILITY, DISSOLUTION & BIOAVAILABILITY

❖ TECHNOLOGY FOR IMPROVED BIOAVAILABILITY

1. SOLID SELF-EMULSIFYING DRUG DELIVERY SYSTEMS

Solid self-emulsifying drug delivery systems (S-SEDDS) are gaining popularity as a novel particle technology to improve solubility behavior of lipophilic drugs and drugs with poor aqueous solubility. S-SEDDS technology is novel in a way that they provide an effective alternative approach to the conventional liquid SEDDS for formulating drugs with poor aqueous solubility. S-SEDDS are formulated by incorporation of liquid or semisolid self-emulsifying (SE) ingredients into powders or nanoparticles by different solidification techniques (eg. spray drying, adsorption to solid carriers, melt granulation and melt extrusion techniques) where the powders or nanoparticles refer to self- emulsifying nanoparticles, dry emulsions and solid dispersions that can be further pro cessed into other solid self-emulsifying dosage forms or can be filled into capsules [48]. S-SEDDS are solid at room temperature and they can be exploited into various dosage forms that are solids with SE properties like SE capsules, SE solid dispersions, dry emulsions, SE pellets and tablets, SE micro sphere, SE nanoparticles, SE suppositories and SE implants. S SEDDS are more desirable than conventional liquid SEDDS which are normally prepared either in soft gelatin capsules. Conventional liquid SEDDS has several limitations in manufacturing process leading to high production costs, are difficult to use, have incompatibility problems with shells of soft gelatin and have problems in storage. S-SEDDS has been widely studied for the enhancement of solubility and dissolution of various poorly soluble drugs and the most common method of S-SEDDS preparation has been spray drying technique plus the use of a solid carrier. Spray drying technique, together with the use of solid carriers like dextran, gelatin, Aerosil® and lactose, has been successfully used to prepare S-SEDDS of drugs like nimodipine, flurbiprofen, dexibuprofen, docetaxel and curcumin with enhanced oral bioavailability .

An alternative method of S-SEDDS preparation was adopted by Agarwal et al. in their study where the powdered self-emulsified lipid formulation of meloxicam was obtained by simple trituration of liquid SEDDS with an adsorbent solid (1:1 mixture of silicon dioxide and magnesium aluminum silicate)in a mortar until a homogenous blend was formed [54].The powdered SEDDS formulation showed higher bioavailability in beagle dogs when compared with that of commercially available tablets. In another study, S- SEDDS of fenofibrate was formulated by solidification of the molten solution of the oily phase, sur factant and co-surfactant and drug mixture with a polymer (PEG 6000), where the S-SEDDS formulation with 10% w/w fenofibrate loading showed as muchas20- foldincrease in the dissolution profile .

"SOLID SELF EMULSIFYING DRUG DELIVER SYSTEM"

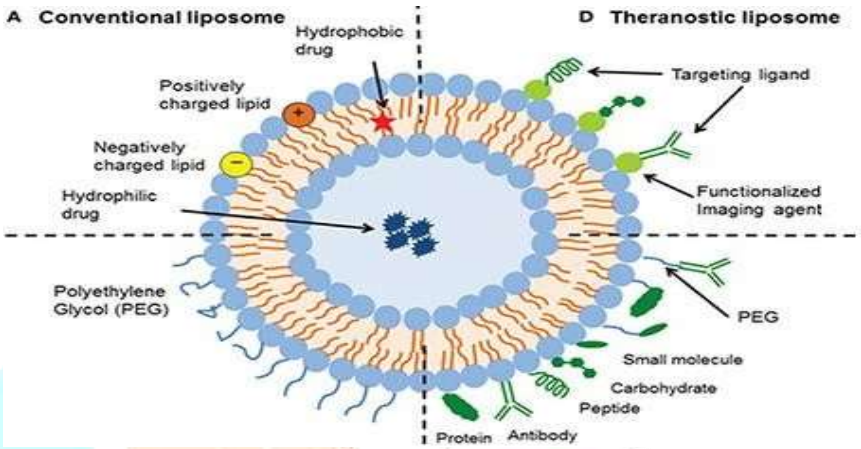
2. FREEZE DRIED LIPOSOMES

Liposomes are phospholipid vesicles, comprising a phospho- lipid bilayer surrounding an aqueous compartment and can dissolve lipophilic drugs in their lipid domain . Because of their biphasic characteristics and diversity in design and composition, they offer a dynamic and adaptable technology for enhancing drug solubility

- Drug encapsulation or entrapment into liposomes result in distinct changes in pharmacokinetic and pharmacodynamics properties of the free drugs, and also helps in decreasing toxicity and increases the therapeutic efficacy in some cases . However, one of the serious limitations with applicability of liposomes as drug delivery systems is associated with its poor stability during storage . The liposomal formulations can thus be stabilized by freeze drying process to obtain dry powders with enhanced stability while maintaining the potency of the incorporated drug. Freeze-dried liposomal formulation of sirolimus (rapamycin) was found to have superior stability after reconstitution when compared to the conventional suspension product of the same drug and the stability of the formulation was even better when dextrose was used as lyoprotectant during freeze-drying .
- It suggests that freeze drying can be an effective approach to deal with the stability problems of liposomal formulations and variety of sugars such as dextrose, sucrose and trehalose can be used as lyo protectants. This type of approach has been reported to be used for liposomal formulation of paclitaxelusing sucroseasa lyoprotectant .
- Freeze-dried liposome system was used to design a novel lyophilized liposome-based paclitaxel formulation that was sterile, stable and easy to use . In another study, paclitaxel incorporated liposomes were pre pared using polyethylene glycol 400 in the hydration medium of liposome which aided the solubilization as well as entrapment efficiency of paclitaxel . The liposomal formulation was found to have enhanced solubility as well as enhanced physicochemical stability after freeze drying
- Therefore, drugs can be formulated with liposomes, a polymer and a lyoprotectant and then freeze-dried to obtain a dry, lyophilized powder. Polymers like PEG are used in some cases for solubilizing the drug in the liposomal solution. A PEGylated liposomal formulation has been reported to enhance the aqueous solubility

Paclitaxel andalso improve the invivo bioavailability in rats.

- Freeze-dried liposome system is a promising approach for formulating drugs with poor aqueous solubility as well as enhancing the stability of liposomal formulation. Liposomal incorporation of poorly soluble drugs followed by freeze drying approach can produce powdered form of the drug that can easily be solubilized in water. This particle technology can be further exploited for formulating wide range of therapeutic agents that are insoluble in water.



"FREEZE DRIED LIPOSOMES"

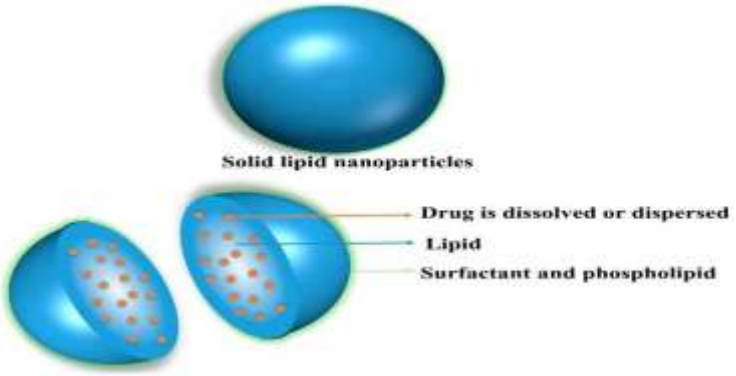
3. SOLID LIPID NANOPARTICLES

Solid lipid nanoparticles (SLNs) are colloidal drug carrier systems which are like nano emulsions, but differing in lipid nature in which the liquid lipid part of emulsionsis replaced by a solid lipid at room temperature such as glycerides or waxes with high melting point .

The interest towards SLN as a novel particle technology is increasing recently because of its potential as an alternative carrier system to traditional colloidal carriers, such as emulsions, liposomes and polymeric micro- and nanoparticles and also due to their possibility to be used in various routes of drug delivery.

- Among various methods of SLN preparation such as HPH (cold and hot homogenization), breaking of o/w micro emulsion, solvent emulsification-evaporation or solvent emulsification diffusion, solvent injection, water-in-oil-in water double emulsion (w/o/w), high shear homogenization and/or ultra sound dispersion, the high pressure homogeni -zation method is considered to be the most effective method of SLN preparation. SLNs prepared by high pressure homogenization have several advantages of narrow particle size distribution, high particle content in the dispersions, avoidance of organic solvents and scale-up feasibility

- Mehnert and Mader,in their review,have described several advantages as well as disadvantages of SLN technology SLN technology is advantageous over other colloidal carrier systems due to its possibility of being formulated as controlled drug release delivery systems and also due to improved drug targeting, increased drug stability, no bio toxicity of the carrier and feasibility of incorporation of both lipophilic and hydrophilic drugs into the carrier. However, certain disadvantages of SLN like low drug-loading capacities and stability problems during storage or administration (gelation, particle size increase, drug expulsion from SLN) cannot be neglected.



“SOLID LIPID NANOPARTICLES”

CLASS-1 DRUGS

The Biopharmaceutics Classification System (BCS) is a framework used to classify drug substances based on their solubility and permeability. Here's a breakdown of BCS Class I drugs:

BCS Class I:

* High Solubility:

* This means the drug readily dissolves in aqueous solutions across a wide pH range.

* High Permeability:

* This indicates the drug easily passes through biological membranes, such as the intestinal

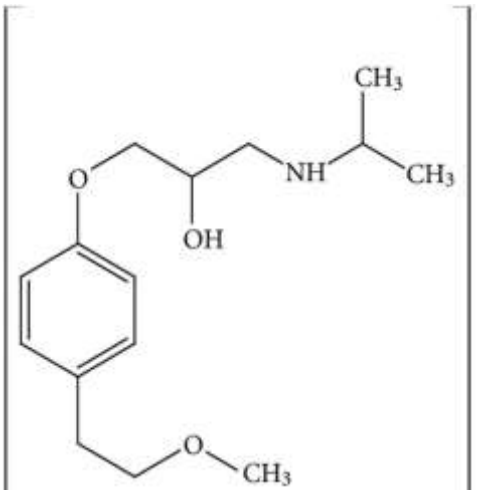
METOPROLOL

FIRST NAME :- Lopressor

SYNONYM :- Beloc ,Betaloc,Seloken,Prelis,Selopral

IUPAC NAME :- 1-[4-(2-Methoxyetyl) Phenoxy] -3- (Propen-2-ylamino) Propan -2- ol

STRUCTURE :-



SOLUBILITY :-

- Very soluble in W[10a]ter .
- Freely soluble in Chloroform, Methylene chloride and alcohol .
- Sightly soluble in Acetone .
- In soluble in Ether .
-

MOLECULAR WEIGHT :- 267.36 g/mol

MELTING POINT :-

Metoprolol Succinate :- 136 ·c- 138 · C Metoprolol Tartrate :- 121 ·c-124 · C

BOILING POINT :- 398 ·C

WATER ABSORPTION RATIO :- 67 % - 87% **WETTING TIME :-** 32SEC TO 64 SEC **INVITRO DISINTEGRATION :-** 18 S TO 125 S

INVITRO DISSOLUTION :- 98.12 to 100.03% WITH IN WATER

IN VITRO DISINTERGRATION TIME :-

- The dis integration time was measured using dis integration test apparatus
- One tablet was placed in each tube of the basket .This basket was immersed in a water bath at 37+20 · C .
- The time required for complete disintegration was recorded with standard deviation.

TABLE VI - Post-compressional parameters for direct compression method

Formulation Code	*In vitro* dispersion time* (sec)	Wetting time* (sec)	Water absorption ratio*	Drug Content* (%)
MT_1	35 ± 1.27	49 ± 1.36	84 ± 1.05	99.18 ± 0.72
MT_2	92 ± 1.25	46 ± 1.18	74± 0.80	99.81 ± 1.07
MT_3	62 ± 1.30	42 ± 1.22	67 ± 1.06	99.54 ± 0.50
MT_4	22 ± 1.37	32 ± 1.29	82 ± 1.28	98.12 ± 0.73
MT_5	18 ± 1.35	28 ± 1.27	87 ± 1.36	99.30 ± 0.87
MT_6	25 ± 1.36	36 ± 1.37	81 ± 1.38	99.23 ± 0.90
MT_7	99 ± 1.31	57 ± 1.32	71 ± 1.34	100.03 ± 1.07
MT_8	116 ± 1.35	64 ± 1.36	75 ± 1.44	99.63 ± 0.39
MT_9	125 ± 1.40	48 ± 1.40	74± 1.31	99.50 ± 0.77

Values expressed as Mean ± SD (n=3).
Formulation code: MT 1 - Formulation containing 3.3% sodium sodium croscarmellose; MT 2 - Formulation containing 6.6% sodium sodium croscarmellose; MT 3 - Formulation containing 10% sodium sodium croscarmellose; MT 4 - Formulation containing 3.3% crospovidone; MT 5 - Formulation containing 6.6% crospovidone; MT 6 - Formulation containing 10% crospovidone; MT 7 - Formulation containing 3.3% sodium starch glycolate; MT 8 - Formulation containing 6.6% sodium starch glycolate; MT 9 - Formulation containing 10% sodium starch glycolate.

IN VITRO DISSOLUTION STUDIES :-

- The in vitro dissolution study was performed using an usp dissolution apparatus type 2 (paddle type) at 100 rpm using 900 ml phosphate buffer ph 6.8 as the dissolution medium at 37 + 0.5 C . Aliquot of dissolution medium were withdrawn and the absorbances of filtered solutions determined by a UV.

  Spectrophotometer at 221.70 nm. Six trials were performed for each batch and average percentage drug release with standard deviation was calculated and recorded.

RESULT AND DISCUSSION :-

- Fast dissolving tablet of tartrate were prepared by a method employing corspovidone ,Sodium starch glycolate and croscarmellose as super dis integrants at different ratios.
- A total of nine formulation were designed . the flow properties of the powder mixture are lmportant for of the uniformity of mass of the tablet; the flow of the powder mixture was analyzed before compression to tablet
- Low Hausener ratio (<1.14) , compressibility index ratio (<15) and angle of response (<28.04) values indicate faimy good flowability of the powder mixture .
- Hardness (3.6kg/cm^2-4.5 kg/cm^2) and friability loss (0.46% -0.73%) indicated that tablet had good mechanical resistance .
- Drugs content was found to be high (>98.12%) in all the tablet formulation .
- Water disintegrantion capacity 18 sec - 125 sec .
- The DSC shows that when the drug metoprolol tartrate was taken to study its properties at higher temperature, it exhibited a melting peak at 126.69 ·C with very little variation compared with the literature-reported temperature . This is probably due to error in experimental determination .The DSC of the optimized formulation showed a melting peak at 120.19 ·C .DSC studies of all formuations indicated that no chemical constituent produced any reaction products .
- In Vitro drug release studies were carried out in phosphate buffer pH 6.8 and the dissolution profile is depicted in. the drug release from the optimized batch (MT5) was 98.12 to 100.3% at 15 min .

CLASS-2 DRUGS

The Biopharmaceutics Classification System (BCS) is a framework used to classify drug substances based on their solubility and permeability. Here's a breakdown of BCS Class II drugs:

BCS Class II:

* Low Solubility:

* This means the drug can’t dissolve in aqueous solutions easily across a wide pH range.

* High Permeability:

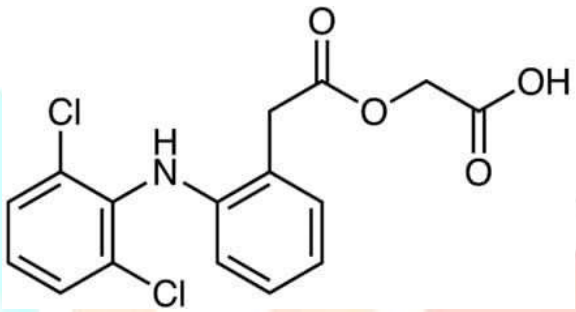
* This indicates the drug easily passes through biological membranes, such as the intestinal

ACECLOFENAC

SYNONYM :- Acecgen, Afamin,Aceflam,Flemac,Bio fenac

IUPAC NAME :- 2-[2-[2-(2,6- Dichoro anilino) Phenyl]Acetyl] oxyacetic acid

STRUCTURE :-



MOLECULAR WEIGHT :- 354 .18 g/mol

SOLUBILITY :- Solubility depends on the solvent and PH .

- It is soluble in organic solvent like ethanol,DMSO and dimethyl formamide
- It is also soluble in phosphate buffer at ph 6.8

MELTING POINT :- 149 · C

- Which is well with in the range of literature specification ,149-150 · C indicating identify and purity .

BOILING POINT :- Aceclofenac is not readily available as it decomposes before reaching a boiling point .

IN VITRO STUDIES OF ACECLOFENAC :-

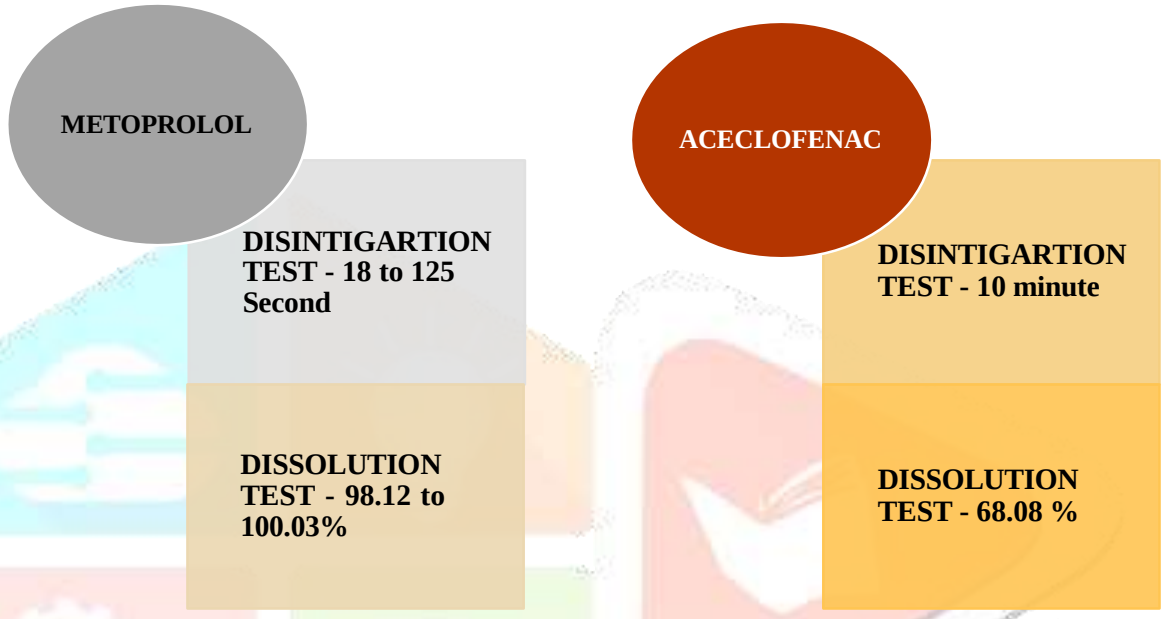
- In Vitro Studies of Aceclofenac The rate of dissolution determines the rate and extent of absorption and subsequent therapeutic outcome of a drug. The factors that affect dissolution include type and concentration of binder, hardness, surface area, distance of diffusion, solubility of the drug, manufacturing process (wet granulation, dry granulation or direct compression) and diluents.Dissolution was another studied important quality control parameters directly related to the absorption and bioavailability of drugs. The study revealed that at different time intervals drug.The release rate was better. After 10 minutes, the release rate of both tablet brands of Aceclofenac was 68.08%Dissolution was another studied important quality control the test started that both the sample of Acelofenac coded A and B have passed the weight variation uniformly test as

specified in the usp

DIS INTEGRATION TIME :-

- The disintegration time of Acelofenac un coated usp tablet have integration time standard was 10 min.

❖ CONCLUSION



- By review different tests of metoprolol and aceclofenac from different review articles we concluded different drugs has different bioavilability,solubility and permeability .
- Metoprolol has high solubility ,high permeability where as Acelofenac has low solubility and high permeability .
- Thus Metroprolol belongs to BCS class1 drugs whereas Acelofenac belong to BCS class 2 drugs.

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