REVIEW ARTICLE

A review on solubility enhancement of Biopharmaceutical Classification System Class II drugs using bilayer tablet technology

Aakash Singh Panwar, Devendra Singh Lodhi, Nirmal Dongre

Department of Pharmaceutics, Institute of Pharmaceutical Sciences, SAGE University, Indore, Madhya Pradesh, India

Abstract

Due to poor solubility, many drugs are not able to produce the desired effect those drugs are categorized into Biopharmaceutical Classification System Class II drugs. For the enhancement of their solubility, cosolvent technology and development of double-layer tablet technology play a very important role. For enhancement of dissolution, the various methods can be used by which we can increase the solubility, by which we can increase the surface area or the methods such as lipid emulsion and microemulsion can be used. The most promising method for developing sustained-release and controlled-release combination formulations is two-layer tablet technology. In this study, different polymer methods can be used for a typical antipsychotics drug for formulation.

Key words: Anti-psychotic drugs, Biopharmaceutical Classification System Class II, Bilayer tablets, controlled release, enhanced solubility, sustained release, tableting technology

INTRODUCTION

According to the available literature, approximately 45% of drugs in the market contain poorly soluble drugs. Therefore, several pharmaceutical companies are currently developing bilayer tablets for a variety of reasons, including patient extension. With advancement in combinatorial chemistry and high-throughput screening, a large number of drug molecules with required pharmacological activity have been developed. Oral route is most commonly employed route of drug administration. Although different route of administration is used for the delivery of drugs, due to flexibility in dosage form design and patient compliance, oral route is preferred. The popularity of the oral route is attributed ease of administration, patient acceptance, accurate dosing, cost-effective manufacturing method, and generally improved shelf-life of the product. The Biopharmaceutical Classification System (BCS) is an experimental model that measures permeability and solubility under prescribed conditions. The original purpose of the system was to aid in the regulation of post-approval changes and generics, providing approvals based solely on *in vitro* data when appropriate. Importantly, since the majority of drugs are orally dosed, the system was designed around oral drug delivery. Waivers (i.e., permission to skip *in vivo* bioequivalence studies) are reserved for drug products that meet certain requirements around solubility and permeability and also rapidly dissolve in the human body. More and more, however, the industry is using the BCS as a tool in drug product development. This system can be used to flag drugs that should not be tested clinically unless appropriate formulation strategies are employed. The influence of each of the three factors, dissolution, solubility, and intestinal permeability on the oral absorption of drugs can be assessed by BCS. FDA has adopted it as a regulating tool in drug product development. The drug product dissolution standards can be set by BCS. This allows for *in vivo in vitro* correlation and can significantly reduce *in vivo* studies. Thus, save time in product development.[1]

Address for correspondence:
Aakash Singh Panwar, Department of Pharmaceutics, Institute of Pharmaceutical Sciences, SAGE University, Indore - 452 027, Madhya Pradesh, India.
Mobile: +91-9617958072.
E-mail: aakashsingh.panwar@gmail.com

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BCS Class Limits Used

1. If a drug substance's highest dose strength is soluble over a pH range of 1–7.5, it is considered very soluble in 250 mL water
2. The medication is considered highly permeable on the basis of mass balance or in contrast with an intravenous dosage, where the extent of absorption in humans is determined to be 90% of the dose given
3. If a volume of 900 mL of a buffer solution is dissolved within 85% of the labeled amount of the drug substance, then the USP apparatus I or II is considered to quickly dissolve the drug product.

The BCS defines three dimensionless numbers to characterize drug substances. They are dose number (D_o), dissolution number (D_n), and absorption number (A_n).The most fundamental view of GI drug absorption is represented by these numbers, which are combinations of physicochemical and physiological parameters.

First, the absorption number (A_n) is the ratio of permeability (P_{eff}) and the gut radius (R) times the residence time (T_{si}) in the small intestine, which can be written as the ratio of residence time and absorptive time (T_{abs}).[2]

Extension to BCS: (BCS Containing Six Classes)

- Bergstrom *et al*. developed a modified BCS and categorized drugs into six classes based on solubility and permeability. The solubility was classified as "high" or "low" and the permeability as "low," "medium," or "high." This new classification was developed from the calculated surface descriptors, on the one hand, and solubility and permeability, on the other. The surface areas related to the non-polar part of the molecule led to good permeability predictions, therefore, it was suggested that these models would be useful for the early detection of absorption profiles of compounds in the early stages of drug discovery so that the necessary modifications to optimize pharmacokinetic parameters
- Dissolution is a process in which a solid substance (drug) goes into solution, that is, the mass transfer of molecules from the solid surface into the liquid phase. Solubility is an intrinsic property of a pharmaceutical substance by which it is chemically formed and physically mixed homogeneously with other substances. To determine the degree of human absorption, the human fasting intestinal solubility parameter (e.g., using FaSSIF) can be used as the primary solubility enhancement parameter
- For Class II drugs, the concept of the soluble-limited absorbable dose (SLAD), this is used on the assumption that their permeability and solubility are compensatory
- As the best valuation tool.
- BCS Classification system Class I: High solubility, high permeability: Generally well-absorbed compounds. Class II: Low solubility, low permeability: Generally poorly absorbed compounds. It has low solubility and high permeability, and its absorption is constrained by its dissolution rate [Figure 1].

Modification of the BCS System

Developmental capacity classification system (Butler and Dressman, 4940): Modification of the BCS system consists of classifying drugs based on factors that affect oral absorption of drugs. In accordance with the principle of quality by design (QbD), the revised system provides a more suitable classification system. The new method is based on the following assumptions:

- To determine the degree of human absorption, the human fasting intestinal solubility parameter (e.g., using FaSSIF) can be used as the main measure of *in vivo* solubility
- For Class II drugs, the concept of SLAD will be used, assuming that their permeability and solubility are compensatory[3]
- As a better way to assess the development risk and critical quality attributes (CQA) of drugs with limited dissolution and absorption rates, dissolution can be expressed as the target drug particle size, rather than a dose/solubility relationship
- Therefore, this modified system deviates significantly from BCS and is mainly used for Class II drugs, adding two subclasses, and emphasizing the prediction of degree rather than oral absorption rate. This revised system, called the Development Capability Rating System (DCS), is not just a regulatory rating system, but to solve problems related to product development. One of the important advantages of this DCS is that it provides formulators with early signals about poorly soluble drugs that can be fully formulated through simple size control, while others require specialized solubilization techniques to obtain complete oral absorption and avoid effects. Drug. Foods related to solubility.

Solubility Enhancement of BCS Class II

Drug solubility of a solute is the maximum quantity of solute that can dissolve in a certain quantity of solvent or quantity of solution at a specified temperature. Various techniques are available to improve the solubility of poorly soluble drugs. These techniques can be categorized into three basic approaches. For poorly water-soluble drugs, various techniques have been used to improve solubility and dissolution rates, including solid dispersion, micronization and lipid formulations as well as melt granulation and direct compaction[Table 1].

Solid dispersion (SD) system

SD is the most widely used technology because it has the potential to improve the bioavailability, low cost, and industrial feasibility of drugs that are difficult to dissolve in water. A SD is defined as a dispersion of one or more active ingredients in an inert carrier or solid matrix prepared by the melt, solvent, or melts solvent method.

The advantages of SD

1. Particle size reduction: In SD, some drug molecules are dispersed in the carrier, representing the final state of particle size reduction. This increases the effective surface area of the drug, resulting in a higher dissolution rate and therefore better bioavailability
2. Improvement of wet ability: As the wet ability of drug particles increases, the dissolution rate also increases significantly. Surfactant vehicles, such as bile salts, significantly increase the wet ability of the drug. In addition, it affects the dissolution profile of the drug through direct dissolution or co solvent effects
3. Increased porosity: The SD produces particles with a very porous structure. The characteristics of the carrier affect the porosity. SDs made from linear polymers have larger and more porous particles than cross-linked polymers and therefore have a high dissolution rate. The higher porosity of SD particles increases the dissolution rate of the drug
4. Drug amorphization: The amorphous forms of drugs that are poorly soluble in water have a higher solubility in water than their crystalline forms. In the case of an amorphous state, no energy is needed to break the crystal lattice during the dissolution process. Dissolution of SD leads to a supersaturated system, in which the drug is in a metastable polymorphic form, with a higher solubility than the more stable crystalline form.

The amorphous composition of drugs with low crystallization energy (low melting point or heat of fusion) is detected by the melting temperature difference between the drug and the carrier, while drugs with high crystallization energy can be obtained by selecting the carrier, and they show specific interaction with them.

Characteristics of SD carriers when selecting a carrier for SD should consider the following criteria:

1. It should be hydrophilic in nature to improve wet ability and solubility
2. It must have a high glass transition temperature to improve stability
3. It must have the minimum water absorption capacity
4. If the drug is prepared using solvent evaporation technology, the drug and vehicle must be soluble in common solvents
5. If the SD is prepared by melting, it should have a lower melting point
6. Must have the ability to form a solid solution with drugs with similar solubility parameters.

Table 1: Dissolution enhancement techniques

Methods which increase the solubility	Methods which increase the surface area	Newer technologies
Modifying the pH of Microenvironment	Micronization	Lipid emulsions
Salt formation of weak acids and weak bases	Use of surfactants (to enhance effective surface area by improvement in wetting)	Microemulsions
Use of solvates and hydrates	Solvent deposition	Self-emulsifying drug delivery systems
Use of selected polymorphic forms	SD	Nanosizing by precipitation
Complexation	Liquid-solid compacts	Cryogenic and super critical fluid technologies
Prodrug approach		Melt granulation
Use of surfactants		Melt extrusion
Sublimation technique		

SD: Solid dispersion

There are some issues that limit the commercialization of SD.

During processing (mechanical stress) or storage (temperature and humidity stress), the amorphous state of the drug can return to the crystalline state and reduce its dissolution rate, thus affecting physical stability. Moisture also plays an important role in the storage stability of the amorphous dosage form because it can promote the flow of the drug and cause the drug to crystallize. In addition, phase separation, crystal growth, and transformation from an amorphous state to a crystalline state or from a metastable crystalline form to a more stable form were observed during storage. This is because the vehicles used in SD absorb water. The SD is soft and sticky in nature, resulting in poor fluidity and compressibility. This can cause problems during processing and the reproducibility of the physical and chemical properties of the final product is poor.[4,5] Many methods exist to prepare solid dispersions, including melting, solvent evaporation, fusion, kneading, spray drying, co-grinding, hot melt extrusion, melt agglomeration, and supercritical fluid (SCF) technology, among others [Table 2].

QbD approach

In recent years, the drug development process has undergone revolutionary changes due to the introduction of the QbD concept. It has transformed the entire paradigm from a univariate empirical understanding to a systematic multivariate approach to establish the systematic quality

Table 2: Methods of preparation and carriers used for SDs

Method of preparation		Carriers used
Advantages	Disadvantages	Polymeric materials: PVP, HPMC, HPMCAS, HPMCP, Eudragit systems (enteric acrylic acid based polymers)
Solvent evaporation		
Ease in preparation	Toxicity	
Feasible scale Up	Residual amount	
Melting		Acids: Citric acid, succinic acid, and tartaric acid
Ease in preparation	Drug degradation for thermosensitive drugs	
Feasible scale up	Low solubility in molten carrier	Sugars: Dextrose, sucrose, maltose, sorbitol, galactose, xylitol, inulin, chitosan, dextrin, cyclodextrin
Anti-solvent		Surfactants: Poloxamer, deoxycholic acid, tweens, spans, Compritol 888 ATO, Gelucire 44/14 and 50/13, sodium lauryl sulfate, phospholipid, polyoxyethylene stearate
Solvent free	Low solubility in CO_2 Limited scale up	Miscellaneous: Urea, urethane, hydroxyalkyl xanthene, pentaerythritol

SD: Solid dispersion

Table 3: Classification of polymers used in sustained-release drug delivery systems (SRDDS)

Polymer characteristics	Material
Insoluble, inert	Polyethylene, polyvinylchloride, ethyl cellulose, methyl acrylates-methacrylate copolymer
Insoluble, erodible	Carnauba wax, stearyl alcohol, stearic acid, polyethylene glycol, castor oil, monostearate triglycerides
Hydrophilic	Methylcellulose, hydroxyethylcellulose, HPMC, sodium CMC, sodium alginate, galactomannose, carboxypolymethylene

Table 4: Classification of antipsychotic drugs

Class	Drug
Phenothiazine	
Aliphatic side chain	Chlorpromazine Triflupromazine
Piperidine side chain	Thioridazine
Piperazine side chain	Trifluoperazine Fluphenazine
Butyrophenones	Haloperidol Trifluperidol Penfluridol
Thioxanthenes	Flupenthioxal4
Other heterocyclics	Pimozide Loxapine is an atypical antipsychotic medication
	Clozapine Risperidone Olanzapine Quetiapine Aripiprazole Ziprasidone

of the final drug. Since January 2012, QbD has become a mandatory requirement for formulation development in this industry. QbD is a broad term that includes predefined target quality and predicted quality by setting required and predetermined specifications. Taking into account, the relevant physical, chemical, physiological, pharmacological, and clinical properties, safe and effective products can be obtained.

- This can be done through extensive investigations of variables related to raw materials, product design, process, and scale. Design of experiments is an important QbD tool that helps to identify factors and their interaction effects (Lionberger *et al*., 268)
- Quality is derived from the design to determine CQA; critical material attributes (CMAs) and critical process parameters, and assist in the development of pharmaceutical products with required characteristics. Therefore, QbD means designing and developing formulas and manufacturing processes to achieve predetermined product quality (Lawrence, 781)
- Determine the source of variability in the manufacturing process and establish the relationship between the recipe and the process. This knowledge is then used to implement flexible and robust manufacturing processes and products of required quality over a period of time (Cui *et al*., 312). A structured process for designing and launching new products, Quality by Design (QbD) is used by many companies. Goods, services, information, and internal processes are all examples of products. Customer needs are met so effectively by a high-quality product that the customer chooses to purchase or use more of it over other sources of meeting those needs [Figure 2].[6]

Tablet Dosage Form

Oral route is most commonly employed route of drug administration. Although different routes of administration are used for the delivery of drugs, due to flexibility in dosage form design and patient compliance, oral route is preferred. The popularity of the oral route is attributed ease of administration, patient acceptance, accurate dosing,

Table 5: Commercially marketed bilayer tablets

S. No. product	Name	Chemical name	Developer
1.	ALPRAX PLUS	Sertraline, Alprazolam	Torrent Pharmaceuticals Ltd.2 is a pharmaceutical company based in the United Kingdom.
2.	Glycomet®-GP2 Forte	Metformin hydrochloride, Glimepiride	USV Limited 3.
3.	Newcold Plus	Levocetirizine hydrochloride, Phenylpropanolamine, Paracetamol	Piramal Healthcare Ltd.
4.	DIAMICRON®XRMEX500	Gliclazide, Metformin hydrochloride	Sedia® Pharmaceuticals (India) Pvt. Ltd.
5.	DIUCONTIN-K®20/250	Furosemide, Potassium chloride	T.C. Health Care Pvt. Ltd.
6.	TRIOMUNE 30	Nevirapine, Lamivudine, Stavudine Cipla Ltd.	
7.	PIOKIND®-M15	Pioglitazone, metformin hydrochloride	Psychotropics India Ltd.
8.	Revelol®-Am 25/5	Metoprolol succinate, Amlodipine besilate Ipca	Laboratories Ltd.

cost-effective manufacturing method, and generally improved shelf-life of the product. Figure 3 helps to dictating different types of layer tablet. The bilayer tablet is a new technology for controlled release formulation development. Bilayer tablets are prepared with one layer of drug for immediate release with the second layer. Later-release drug layer, either as a second dose or in extended-release form.As well as for the sequential release of two drugs in combination, a multi-layer tablet can be used for the sustained release of a tablet in which one layer is intended for immediate release as a loading dose and the second layer as a maintenance dosage [Figure 3] There are several techniques of conventional drug delivery system where tablets, capsules, pills, and liquids are used as drug carrier. Among them, solid formulation does not require sterile conditions and is, therefore, less expensive to manufacture. The tablet is the most widely used dosage form because of its convenience in terms of self-administration, compactness, and ease in manufacturing. Tablets are solid dosage forms containing medicinal substances with or without suitable diluents. According to Indian Pharmacopoeia, pharmaceutical tablets are solid, flat, or biconvex dishes, unit dosage form, prepared by compressing a drugs or a mixture of drugs, with or without diluents. They are varying in size and weight, depending on amount of medicinal substances and the intended mode of administration. It is most popular dosage form and 70% of the total medicines are dispensed in the form of tablet.[7]

Oral Tablets: 1. for example, a compressed tablet. The second Paracetamol tablet. For example, a chewable tablet. Tablets used in the oral cavity: 1. Take a buccal tablet, for example Taking two vitamin-c tablets Such a tablet can be taken sublingually, for example Tablets dissolve quickly in the stomach and are absorbed quickly, providing a quick-acting dose of Vicks Menthol. To dissolve on the tongue, orally disintegrating tablets must be swallowed. Tablets that are sublingual are placed under the tongue and are swallowed. Liquid is dissolved in effervescent tablets, which are then consumed [Figure 4].

Sustain Release

System designed to achieve a long-term therapeutic effect by continuously releasing the drug over a long period of time after a single administration. The primary goal of treatment is to achieve steady-state blood levels where the therapeutic effect is non-toxic for a long period of time.

- The design of an appropriate dosing regimen is an important factor in achieving these goals. A sustained-release formulation is a formulation in which one or more drugs are released systemically or locally to a specific target organ in a predetermined pattern and continuously for a certain period of time. Sustained-release dosage forms allow better control of plasma drug levels, lower doses, fewer side effects, increased efficacy, and more consistent delivery[7]
- The difference between controlled release and sustained release is controlled drug delivery, which delivers the drug at a given rate during a specific period of time. Controlled release is a complete dimensionless emission of drug release overtime, regardless of concentration. To achieve the desired therapeutic response more quickly, some of the drug (initial volume) is released immediately and the rest (retention volume) is sustained as defined as the type of formulation that is released slowly. The release formulation, which lasts for a long time, but by achieving a therapeutic level that is not maintained at a constant level. Sustained release means slow release of the drug over a long period of time[8]
- It may or may not be controlled by allowing rationality in the SR dosage form of design. The main purpose of pharmaceutical design is to face uncertain fluctuations and to optimize drug delivery to achieve control of therapeutic efficacy. In an environment, where drug release occurs
- This is usually associated with maximum drug availability by trying to reach the maximum rate and range of drug absorption. However, the control of drug action through

the drug means the control of bioavailability to reduce the absorption rate of the drug. Sustained-release, sustained action, prolonged action, controlled release, prolonged action, and time release dosage form were designed to achieve a prolonged therapeutic effect by continuously releasing the drug over a long period of time after drug administration. A term used to identify a drug delivery system. Single dose

- For inject able formulations, this period can vary from days to months. However, for oral dosage forms, this period is measured on an hourly basis and is highly dependent on the residence time of the dosage form from the gastrointestinal tract. Over the past few years, existing drug dosage forms have been rapidly replaced by new and new drug delivery systems. In particular, controlled release/sustained-release dosage forms have become popular in modern therapies
- The basis for sustained-release drug delivery is to use a new drug delivery system or modify the molecular structure or physiological parameters inherent in the route of administration of choice to alter the pharmacokinetics and pharmacodynamics of the drug. That is
- The duration of action should be a design characteristic of the rate-controlled dosage form, rather than the inherent kinetic properties of the drug molecule. Therefore, optimal design of sustained-/controlled-release systems requires a thorough understanding of pharmacokinetics. Pharmacodynamics of drugs[9]

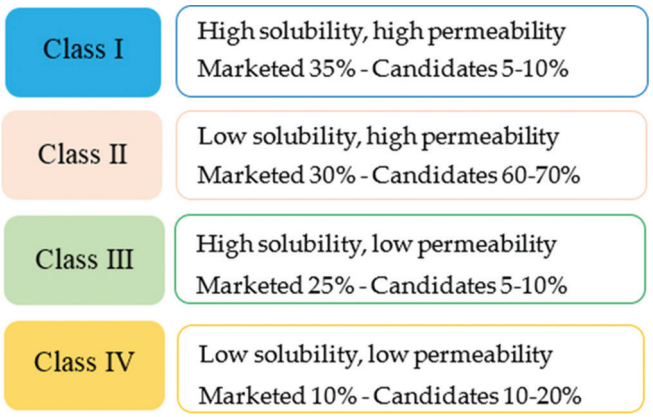

Figure 1: BCS classification

- When the drug is administered in the existing dosage form, fluctuations in drug concentration occur at the site of action (peak and valley pattern), occurring in the systemic circulation and tissue compartment. The sustained-release system includes all drug delivery systems to achieve slow release of the drug over a long period of time
- Whether the system is a temporal and/or spatial characteristic of drug release in the body, that is, the target tissue or cell of the system considers it a controlled release system.
- This system's primary goal is to ensure patient safety and efficacy, as well as to improve patient compliance. Drug levels are better controlled and less frequent dosing is used to achieve this goal Pharmaceutical theory suggests that the best way to reduce the ratio of plasma maximum concentration (Cmax) to plasma minimum concentration (Cmin) is to reduce the drug's physiochemical properties, physiological factors, and manufacturing variables to zero. Upon achieving steady state in these conditions, drug concentrations will stabilise [Figure 5].

Advantages of sustain release dosage form

a. Patient adaptability generally a lack of compliance is observed in long-term treatment of chronic diseases. All medications depend on the patient's ability to adhere to the treatment. Patient compliance is influenced by a combination of factors, including awareness of the disease process, patient confidence in treatment, and understanding of the need to adhere to strict treatment schedules. Furthermore, the complexity of the treatment regimen, the cost of treatment, and the magnitude of the local and/or systemic side effects of the formulation. The problem of patient lack of compliance can be addressed to some extent by administering sustained-release drug delivery systems

b. Reduction "seesaw:" Administration of drugs in conventional formulations (except by intravenous infusion at a constant rate) can often result in a "ball-to-ball" pattern of drug concentrations in body circulation and tissue compartments. The magnitude of these fluctuations depends on drug dynamics such as absorption

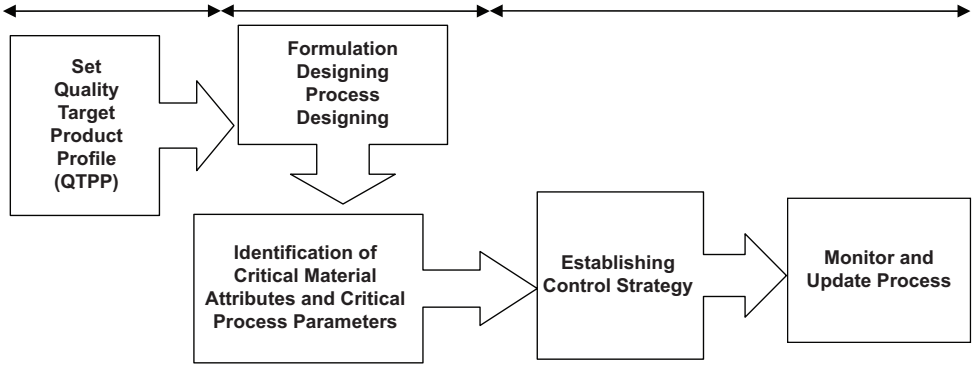

Figure 2: Overview of QbD

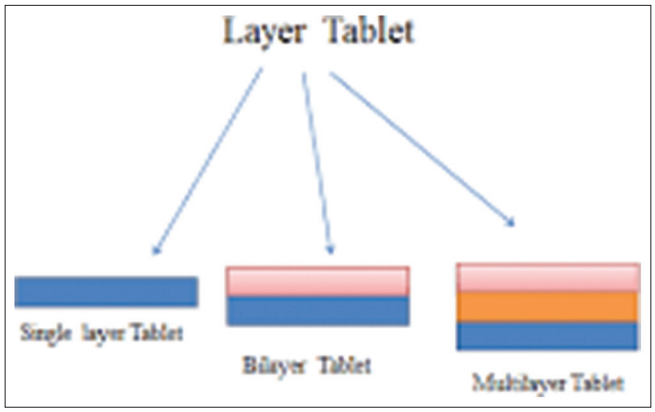

Figure 3: Classification of layer tablet

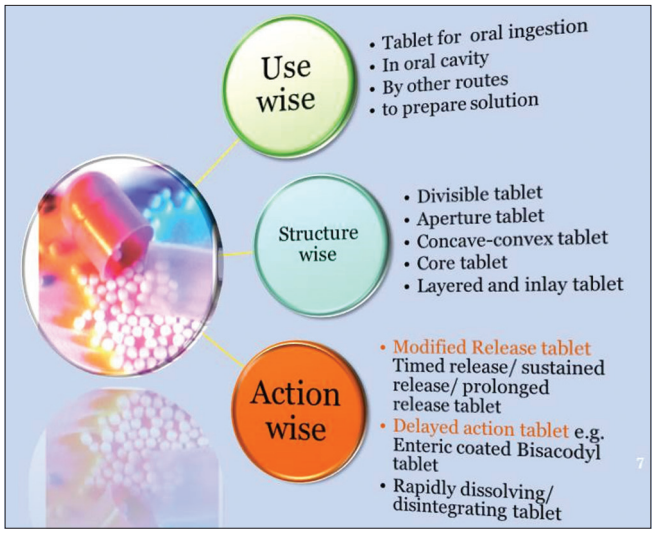

Figure 4: Classification of tablet

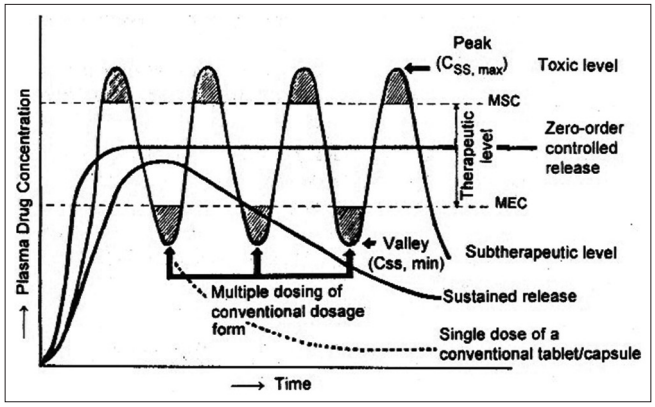

Figure 5: A hypothetical plasma concentration versus time profile

rate, distribution, deletion, and dosing interval. For drugs with a biological half-life of <4 h, the "seesaw" or "peak and valley" pattern is even more pronounced because the prescribed dosing interval is less than about 4 h. A well-designed sustained-release drug delivery system can significantly reduce the frequency of drug administration and maintain stable blood circulation and drug levels from cells in target tissues[10]

c. Decrease in total volume: The continuous release drug delivery system repeatedly used less of a total of drugs to treat the disease. By reducing the total dose of the drug, a reduction in systemic or local side effects is observed. This will also lead to a bigger economy[11]
d. Improving treatment efficiency: Optimal treatment of disease requires effective delivery of active drugs to the tissues and organs to be treated. Often, doses in excess of those required in cells must be used to achieve the required therapeutically effective concentrations. Unfortunately, this can lead to undesirable toxicological and immunological effects on non-target tissues. The continuous release of dosage forms provides better control of acute or chronic disease
e. Reduces local and systemic side effects and reduces gastrointestinal irritation
f. Better reduction of drug use in the total amount consumed
g. Improve the effectiveness of treatment; optimize therapy, blood concentration more uniform
h. Reduced fluctuations in drug concentration and therefore more uniform pharmacological response, faster treatment and control of disease, and less reduction in drug activity with chronic use
i. The method used to achieve sustained release may improve the bioavailability of certain drugs, such as those sensitive to enzymatic inactivation, which can be protected by encapsulation in a polymeric system suitable for sustained release
j. Although the initial unit cost of extended release products is often higher than that of conventional dosage forms due to the special nature of these products, the average cost of extended period therapy may be lower
k. Savings can also reduce the length of treatment and hospital stay[12]

Opportunities and markets

The oral dosage form market is the largest sector in the industry and the market today, but this is no reason for market makers to increase their shipments and make efforts. The force of extended delivery times and the benefit that the business has toward the elderly to make their products safe and effective is very surprising. The oral dosage form drug distribution market was 135 billion in 2018 in the era of globalization and has since grown to 140 billion in 2019. Forecast for 2019 is 200 billion dollars, with growth rate compound annual rate of 8.2% for 6 years. The largest market segment is controlled target drug delivery systems, valued at 60 billion in 2018, and expected to reach 100 billion by 2020 at a CAGR of 10%. The latter market share is estimated to reach 38 billion in 2019 and 46 billion in 2018, at a CAGR of 5%, due to the problem of short half-life. Administration of sustained-release drugs may involve dosing to improve adherence.[13]

The challenges of the sustainable development formula dumping

Dumping is a phenomenon in which a relatively large amount of a drug in a sustained-release formulation is released rapidly, introducing large amounts of a drug potentially toxic to the system circulation.

1. Overdose can be fatal in the case of potent drugs with an arrowed therapeutic index, such as phenobarbital
2. Limited options for determining the desired dose in the unit. Dosage adjustment in conventional dosage forms is much simpler. For example, a tablet can be divided into two fractions. In the case of extended-release dosage forms, this appears to be much more complicated. If the dosage form is broken, sustained-release properties may be lost
3. Weak *in vitro-in vivo* correlation: In sustained-release dosage forms, the drug release rate is intentionally reduced to achieve drug release, possibly over a large area of the gastrointestinal tract. The so-called "absorption window" appears here and it can lead to poor absorption of the drug in the living organism despite its excellent *in vitro* release properties
4. Patient variability: The time it takes to absorb the drug from the dosage form may vary. The concomitant administration of other drugs, the presence or absence of food, and the duration of residence in the gastrointestinal tract vary from patient to patient. It also leads to differences in clinical response between patients.[14]

Criteria for forming a SUSTAINABLE formulation

a. Expected half-life: The half-life of a drug is an indicator of its lifespan in the body. If the drug has a short half-life (<2 h), the dosage form may contain large amounts of the drug. On the other hand, drugs with half-lives of 8 h or more are good enough for sustained-release drug delivery systems and are generally not needed in such cases hours
b. High therapeutic index: Drugs with a low therapeutic index are not suitable for incorporation into sustained-release formulations. If the system breaks down in the body, dumping can occur leading to death, for example, diflucan toxin
c. Small doses: While the strength of a drug in conventional dosage form is high, its suitability as a candidate for sustained release has not been seriously determined. This is mainly due to the fact that the size of a unit dose of the sustained-release formulation would become too large to be used without difficulty[15]
d. Desirable absorption and solubility characteristics: Drugs which are poorly soluble in water often dissolve at a slow rate, making it difficult to incorporate these compounds into sustained-release formulations. Desirable absorption and solubility characteristics: Drugs that are poorly soluble in water are often dissolved at a slow rate. It is, therefore, impractical to incorporate such compounds in sustained-release formulations and may reduce the overall effectiveness of absorption[16]
e. First-passage clearance: As noted earlier in the extended delivery system limitations, the delivery of the drug at the desired concentrations is severely impeded in the event of drug exposure. Through extensive hepatic metabolism, when used sustainably. Release forms.[16] Hydrogels are polymers that expand without dissolving when placed in water or other biological fluids, which are used in most swelling-controlled release systems. At equilibrium, these hydrogels typically contain 60–90% fluid and 10–30% polymer. Degradable polymers are attractive materials for drug delivery systems, tissue-engineering scaffolds, implants, and surgical materials, among other applications. There are many degradable polymers, but PLGA is the most widely used due to its long clinical history and favourable controlled-release and degradation behaviour [Table 3]

Mechanism of drug release from matrix

Drug in the outside layer exposed to the bathing solution is dissolved first and then diffuses out of the matrix. This process continues with the interface between the bathing solution and the solid drug moving toward the interior. It follows that for this system to be diffusion controlled, the rate of dissolution of drug particles within the matrix must be much faster than the diffusion rate of dissolved drug leaving the matrix.

Derivation of the mathematical model to describe this system involves the following assumptions:

a. A pseudo-steady state is maintained during drug release
b. The diameter of the drug particles is less than the average distance of drug diffusion through the matrix
c. The bathing solution provides sink conditions at all times. The release behavior for the system can be mathematically described by the following equation:

$$DM/Dh = C_O . Dh\text{-}C_S/2 \quad (1)$$

Where,
DM = Change in the amount of drug released per unit area
Dh = Change in the thickness of the zone of matrix that has been depleted of drug
C_O = Total amount of drug in a unit volume of matrix
C_S = Saturated concentration of the drug within the matrix.

Diffusion Theory

$$DM = (D. C_S/h).Dt \quad (2)$$

Where, Dm = Diffusion coefficient in the matrix,
h = Thickness of the drug-depleted matrix,
Dt = Change in time.

By combining Equations 1 and 2 and integrating;

$$M = {}_S . Dm. (2C_O\text{-}C_S). t]^{1/2} \quad (3)$$

When the amount of drug is in excess of the saturation concentration, then:

$$M = {}_{S}.\ Dm.\ C_{O}.\ t^{1/2} \quad (4)$$

Equations 3 and 4 relate the amount of drug release to the square root of time. Therefore, if a system is predominantly diffusion controlled, then it is expected that a plot of the drug release versus square root of time will result in a straight line. Drug release from a porous monolithic matrix involves the simultaneous penetration of surrounding liquid, dissolution of drug, and leaching out of the drug through tortuous interstitial channels and pores.

The volume and length of the opening must be accounted for in the drug release from a porous or granular matrix:

$$M = Ds.Ca.p/T.(2C_{O} - p.C_{a})\ t]^{1/2} \quad (5)$$

Where,
p = Porosity of the matrix, t = Tortuosity, Ca = Solubility of the drug in the release medium
Ds = Diffusion coefficient in the release medium, T = Diffusion path length for pseudo-steady state, the equation can be written as:

$$M = C_{a}.\ C_{O}\ (p/T)\ t^{1/2} \quad (6)$$

The total porosity of the matrix can be calculated with the following equation:

$$P = pa + Ca/\rho + Cex/\rho ex \quad (7)$$

Where,
P = Porosity, ρ = Drug density, pa = Porosity due to air pockets in the matrix
Pex = Density of the water soluble excipients, Cex = Concentration of water-soluble excipients.For the purpose of data treatment, Equation 7 can be reduced to:

$$M = k.\ t^{½} \quad (8)$$

Where, k is a constant so that the amount of drug released versus the square root of time will be linear if the release of drug from matrix is diffusion controlled. If this is the case, the release of drug from a homogeneous matrix system can be controlled by varying the following parameters.

- Initial concentration of drug in the matrix
- Porosity
- Tortuosity
- Polymer system forming the matrix
- Solubility of the drug.

MATRIX EROSION

The drug release is caused by degradation of the polymer surface.[17]

In the last decade, interest in developing a combination of two or more active pharmaceutical ingredients (API) in a single dosage form has increased in the pharmaceutical industry, promoting patient convenience and compliance. Bilayered tablets can be a primary option to avoid chemical incompatibilities between APIs by physical separation and to enable the development of different drug release profiles. As a result of active (enzyme) or passive (hydrolysis) degradation, polymers can be eroded on the surface or in the bulk Figure 6 Polymer degradation occurs only at the surface of a surface erosion process, and the rate of degradation is proportional to surface area. This predictability is ideal for many drug delivery applications. As a result of surface erosion, the polymer degrades from the exterior surface of the material.

Double-layer tablets are defined as a new technology for the development of drug formulations with sustained and rapid release, resulting in drug effectiveness [Figure 7]. As a double-layer tablet, it was developed to achieve drug compatibility and facilitate the separation of drugs and drug components to develop various drug releases. The development of a double-layer tablet requires the same drug formulation. The double-layer tablet is not only suitable for the sequential release of a combination of two drugs but also suitable for the sustained release of a tablet with an immediate release layer. Dose loading and the second layer serve as a maintenance dose. Therefore, the use of double-layer tablets is a very novel aspect of antihypertensive, diabetes, anti-inflammatory, and analgesic drugs, in which combination therapy is often used. Due to various reasons, including patent extensions, several pharmaceutical companies are developing double-layer tablets. Double-layer film is a better and more useful technology, which solves the shortcomings of single-layer film. At present, several pharmaceutical companies are developing double-layer tablets. To reduce capital investment, existing but improved tablet presses are often used to develop and produce such tablets.

Over the past decade, the pharmaceutical industry has increased interest in developing combinations of two or more APIs in a single dosage form (double-layer tablet), thus improving patient comfort and compliance. Double-layer tablets can be used as the primary option to avoid chemical incompatibility between APIS through physical separation and to develop different drug release profiles (i.e., release and sustained release). The double-layer tablet is suitable for the sequential release of the combination of two drugs, separating two mutually incompatible substances, and it can also be used for the combined sustained release and rapid release treatment of the same drug in different layers.

- Requires double-layer film
- For the administration of a fixed-dose combination of different APIs, prolong the treatment time with the drug
- Product life cycle, oral mucosa adhesion delivery system, manufacture of a new drug delivery system
- All oral dosage forms have the highest chemical and microbiological stability

- Coating technology can mask unpleasant odor and bitterness
- Flexible concept
- They are unit dosage forms and have the greatest function of all oral dosage forms, achieving the highest dosage precision, and the least content variability
- Easy to swallow and rarely causes hanging.

The die tool is ejected from the press at the end of the manufacturing process, completing the manufacturing process. Through the use of raising and ejecting cams, the upper and lower punches are lifted. The die cavity is ejected from the die cavity by the cams, which punch the tablet [Figure 8].

The ideal characteristics of the double-layer sheet

- The double-layer sheet should have elegant product characteristics without defects such as chips, cracks, discoloration, and contamination.
- Must be strong enough to resist mechanical impact during the production process. • Packaging, transportation, and distribution.
- It must be chemically and physically stable to maintain its physical properties over time. • Double-layered tablets must be able to release drugs in a predictable and repeatable way for mass production, such as chews and floating tablets for the delivery of drugs retained in the stomach
- Control the rate of delivery of one or two different APIs
- Change the total available surface area of the API layer by interleaving the API layer with one or two active layers to achieve a swell able/erodible barrier. A modified version
- Separate incompatible APIs and use the functional properties of the other layer (such as permeability) to control the release of API from one layer
- The drug must be administered at a rate determined by the body during treatment. It should only guide the active entity to the place of action. This is achieved through the development of new and diversified modified drug release dosage forms, such as controlled release dosage forms, extended-release dosage forms, sustained-release dosage forms, fixed point drug delivery systems.[18]

Advantages of the two-layer tablet dosage form

- Compared to all other oral dosage forms, the price is lower
- Sequential release of two drug combinations separates the two incompatible substances also suitable for sustained-release tablets, where one layer serves as the starting dose and the second layer serves as the maintenance dose
- If the drug can be incorporated into the non-adhesive top layer, the release can be almost unidirectional. Its delivery occurs throughout the oral cavity
- Product identification is quick and easy, no additional steps are required when using raised and/or monogram perforated surfaces.[19]

General characteristics of the double-layer tablet dosage form

- The double-layer tablet should have elegant product characteristics and be free of defects such as chipping, cracking, discoloration, and contamination
- Must be strong enough to withstand mechanical shocks during production, packaging, transportation, and distribution
- Must be chemically and physically stable to maintain its physical properties overtime. The Bilayer tablet must be able to release the drug in a predictable and repeatable manner
- It must have a chemically stable service life, so as not to follow the change of the agent.[19]

GMP and Quality Requirements

- To produce GMP compliant and verified quality double-layer tablets, it is important to choose a double-layer tablet press that can prevent clogging and separate the two independent layers that make up the double-layer tablet
- Provide sufficient hardness for tablets
- Avoid cross-contamination between the two layers
- Create a clear visual separation between the two layers
- High performance
- Precise and separate control of the weight of the two layers. Uses various skins on the bilayer tablet. Floating drug delivery systems (FDDSs) from a technical and formulation standpoint, the development of floating drug delivery systems (GRDF) should be simple and consistent
- Methods for developing FDDSs: The following methods are used to design floating dosage forms for single-unit and multi-unit systems
- Stomach double float tablets: These are also two-layer compressed tablets, namely, (i) immediate release layer and (ii) sustained-release layer. Multi-unit floating tablets: These systems consist of sustained-release "seed" tablets surrounded by a double layer
- The inner layer is made up of an effervescent agent, while the outer layer is made up of a swell able film layer. When the system is immersed in the dissolution medium at body temperature, it immediately sinks and then forms an inflated pellet like a balloon, which floats due to its low density. Formulation method: Having a predefined system that can make data-driven decisions, which is necessary for effective drug development. In addition to the BCS category, the inputs for such systems include detailed solubility curves, polymorphism state, required dosage forms, and target dose, and there is much more to consider as the manufacturing of multilayer tablets involves many often incompatible products, additional

equipment, and many prescription and operational challenges.[20]

CNS Disorder

Historically, policy manufacturers and researchers have used mortality statistics because the principal live of the seriousness of unwellnesss, supported that countries and organizations have launched disease management programs. Mortality statistics alone, however, underestimate the suffering caused by diseases which will be nonfatal however cause substantial incapacity. Several neurologic and medical specialty conditions belong during this category. The absence of some neurological disorders from lists of leading causes of death has contributed to their semi-permanent neglect. Once the relative seriousness of diseases is assessed by time lived with disability instead of by mortality, many neurologic disorders seem as leading causes of suffering worldwide. The World Health Organization information counsel that neurological and medical specialty disorders are a crucial and growing cause of morbidity. The magnitude and burden of mental, neurological, and behavioral disorders are huge, moving over 450 million folks globally. In line with the world burden of unwellness report, 33% of years lived with incapacity and 13% of disability-adjusted life years are because of neurological and psychiatric disorders that account for four out of the six leading causes of years lived with incapacity.

Central nervous system is the part of the nervous system consisting of the brain and spinal cord. Any alteration or degeneration of nerves causes CNS disorders. Mainly there are two types of disorders associated with CNS that is neurological and psychological. Neurological disorders such as Parkinson's disease, multiple sclerosis, Alzheimer's disease, epilepsy, Huntington's disease, and psychological disorders such as anxiety, depression, psychosis, and bipolar disorders.[16]

Schizophrenia

It is a chronic disease of the brain. Many people with schizophrenia are disabled by their symptoms. People with schizophrenia can hear voices that others cannot hear. They may think other people are boring enough to hurt them. Sometimes, they just do not make sense when they say it. Diseases make it difficult to care for them. Signs for schizophrenia usually begin between the ages of 16 and 30. Men often develop symptoms at an earlier age than women. People generally do not get schizophrenia after age 45. Schizophrenia can be treated with medication and the help of family members or caregivers. Although symptoms have improved, schizophrenia requires long-term care. For psychiatric disorders, effective management of signs and symptoms is needed at low doses. The second-generation antipsychotics have fewer side effects and are safer to use. Inject able drugs suffer from disadvantages such as "slow dose titration," time to reach steady state, application side, and frequent visits to the clinic. They are also invasive, preventing patient adherence, which is a major concern because it often leads to relapse morbidity, mortality, and significant financial burden on families. The world faces a wide range of mental health disorders, including depression, bipolar disorder, schizophrenia and other psychoses, dementia, cognitive impairment, and mental disabilities. Develop as autism. Schizophrenia is a severe mental disorder that affects humans, defined by intense disruption of thinking, language, emotions, basic cognitive processes, and consciousness. It involves mental experiences, such as hearing voices or delusions. Thus, it affects performance at different social and occupational levels. According to the WHO, schizophrenia is a serious mental disorder that affects more than 21 million people worldwide. It also comes with a range of financial costs including direct treatment costs as well as non-health-care costs such as lost wages, poor job performance, and more.

Causes of schizophrenia

a. Genetic factors, because the disease is familial
b. Atmospheres, such as worms and prenatal feeding problems
c. Brain structure and brain chemistry are not the same.

Symptoms of schizophrenia signs of schizophrenia range from acute to chronic. There are two main types of indications.

1. Positive symptoms are "additional" disturbances to a person's behavior. • Illusion misconceptions: A person may believe that someone is watching them or that they are someone they know well.
   - Hallucinations – seeing, smelling, smelling, hearing, or smelling things that are not really there. It is more common to hear imaginary speeches that give instructions or comments to the individual. • Disturbed thoughts and speech pass from one topic to another in a ridiculous way. Individuals can make their own arguments or make noise.
2. Negative symptoms are "lost" abilities of a person's behavior. • Refusal in public • Life-threatening apathy • Lack of energy or creativity • Apathy

Treatment of schizophrenia: There is no cure for schizophrenia. However, there are two treatments that can help manage symptoms: Medications and psychosocial treatments. Many antipsychotics can be of benefit, so the type of medication depends on each patient. Sometimes, a person has to try different medications to see which one is best for them. Medicines can cause side effects. Most of the time, the negative effects subside after a few days. Take more time.[15]

Risk factors for developing schizophrenia:

- Biological factors
- Family history (genetics) – A family history of mental

disorders and certain personality disorders associated with an increased risk of schizophrenia

- Physical brain defects – There is some evidence that people with schizophrenia have certain changes in the shape of the brain (enlarged ventricles, smaller hippocampus)
- Chemical imbalance – Some evidence suggests that the chemical systems involved in the neurotransmitters dopamine and glutamate are involved. Neurodevelopment factors
- Personal characteristics of poor social and communication skills, as well as interpersonal skills. • Environmental stress
- • Schizophrenia is not a stress-related illness, but stress can interact with other risk factors to cause acute episodes (psychotic) of disease. Stressful activities and events include substance use, work/school problems, and rejection.

An antipsychotic drug of atypical type, also known as a second-generation antipsychotic drug. In the 1990s, the FDA approved the use of these new medications. Antipsychotic drugs are classified as typical or atypical based on their extrapyramidal effects. This study, however, attempted to classify antipsychotic drugs based on gene expression in the frontal cortex, since it is one of the most important regions for antipsychotic actions. Antipsychotics such as chlorpromazine and thioridazine were chosen, while olanzapine and quetiapine were chosen as atypical antipsychotics [Table 4].

Assessment Method

1. Tablet thickness and size the thickness and diameter of the tablet are important for size consistency. A variable call is used to measure thickness and diameter
2. Hardness: The resistance to transport or to breaking of tablets under the conditions of storage, transport, and handling before use depends on their hardness. The hardness of the tablets of each formulation was measured with a Monsanto hardness tester. The hardness is measured generally at 3.5 kg/cm^2
3. Friability is the measure of tablet strength. Twenty tablets were weighed accurately and placed in the tumbling apparatus that revolves at 25 rpm, dropping the tablets to a distance of six inches with each revolution. After 4 min, the tablets were weighed and the percentage loss in tablet weight was determined. % loss = [(Initial weight of tablets–Final weight of tablets)/Initial weight of tablets]/Initial weight of tablets 100. Uniformity of weight: Twenty tablets were selected at random and the average weight was calculated
4. The weight variation was calculated and compared to the standards. Manufacturing process of bilayer tablet manufacturing processes such as wet granulation/roller compaction and the addition of binders increase the level of complexity in understanding the critical factors governing compression and tablet breaking force. Thus, the tablet breaking force and the tablet's propensity for delaminating/capping either during manufacturing or during storage need to be carefully observed. Apart from the CMAs of individual components and final blend, the tablet press has a large influence on the manufacture of multilayer tablets. The level of pre-compression force, punch velocity, consolidation time (time when punches are changing their vertical position in reference to the rolls as the distance between the punch tips is decreased), dwell time (time when punches are not changing their vertical position in reference to the rolls), relaxation time (time when both punches are changing their vertical position in reference to the rolls as the distance between the punch tips increases before losing contact with the rolls), and the applied force can have a significant effect on the CQA. For instance, the extent of compact densification and resistance to compressibility within the die cavity was impacted by compaction pressure and the punch velocity[14]
5. General appearance: The overall appearance of a tablet, as well as its visual identity and overall elegance, is critical for consumer acceptance. Tablet's size, shape, color, presence or absence of an odor, taste, surface texture, physical flaws and consistency, and legibility of any identifying marking
6. Size and shape: The size and shape of the tablet can be dimensionally described, monitored, and controlled
7. Tablet thickness: Tablet thickness is an important characteristic in reproducing appearance and also in counting using filling equipment. Some filling equipment utilizes the uniform thickness of the tablets as a counting mechanism. Ten tablets were taken and their thickness was recorded using a micrometer
8. Weight variation: Standard procedures are followed as described in the official books. Friability friction and shock are the forces that most often cause tablets to chip, cap, or break
9. The friability test is closely related to tablet hardness and is designed to evaluate the ability of the tablet to withstand abrasion in packaging, handling, and shipping. It is usually measured by the use of the Roche facilitator. A number of tablets are weighed and placed in the apparatus where they are exposed to rolling and repeated shocks as they fall 6 inches at each turn within the apparatus. After 14 min of this treatment or 100 revolutions, the tablets are weighed and the weight is compared with the initial weight. The loss due to abrasion is a measure of the tablet's friability. The value is expressed as a percentage. A maximum weight loss of not more than 1% of the weight of the tablets being tested during the friability test is considered generally acceptable and any broken or smashed tablets are not picked up. Normally, when capping occurs, friability values are not calculated. A thick tablet may have less tendency to cap, whereas thin tablets of large diameter often show extensive capping, thus indicating that tablets with greater thickness have reduced internal stress. The

loss in tablet weight is a measure of friability and the percentage friability of the tablets was measured.

10. Stability study (temperature dependent): The bilayer tablets are packed in suitable packaging and stored under the following conditions for a period as prescribed by ICH guidelines for accelerated studies. The tablets were withdrawn after a period of 15 days and analyzed for health issues.
11. Some examples of bilayer tablets containing a combination of drugs. Increase patient compliance with Metformin hydrochloride and Pioglitazone by reducing the frequency of administration Diltiazem hydrochloride + Lovastatin Improve patient compliance and disease management, as well as being in [Table 5].

CONCLUSION

The BCS is an experimental model that measures permeability and solubility under prescribed conditions. The original purpose of the system was to aid in the regulation of post-approval changes and generics, providing approvals based solely on *in vitro* data when appropriate. The work will contribute to demonstrating the feasibility of development of a bilayer tablet of BCS Class II drug formulation comparable to the commercial formulation. Bilayer tablet in which one layer will provide a fast release to show an immediate effect and the other layer will provide a sustained release of the drug and will be useful for maintaining the drug concentration in the diseased state and is helpful for patients and the next generation. Such a phenomenon could be studied and used to help with drug product development.[18]

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