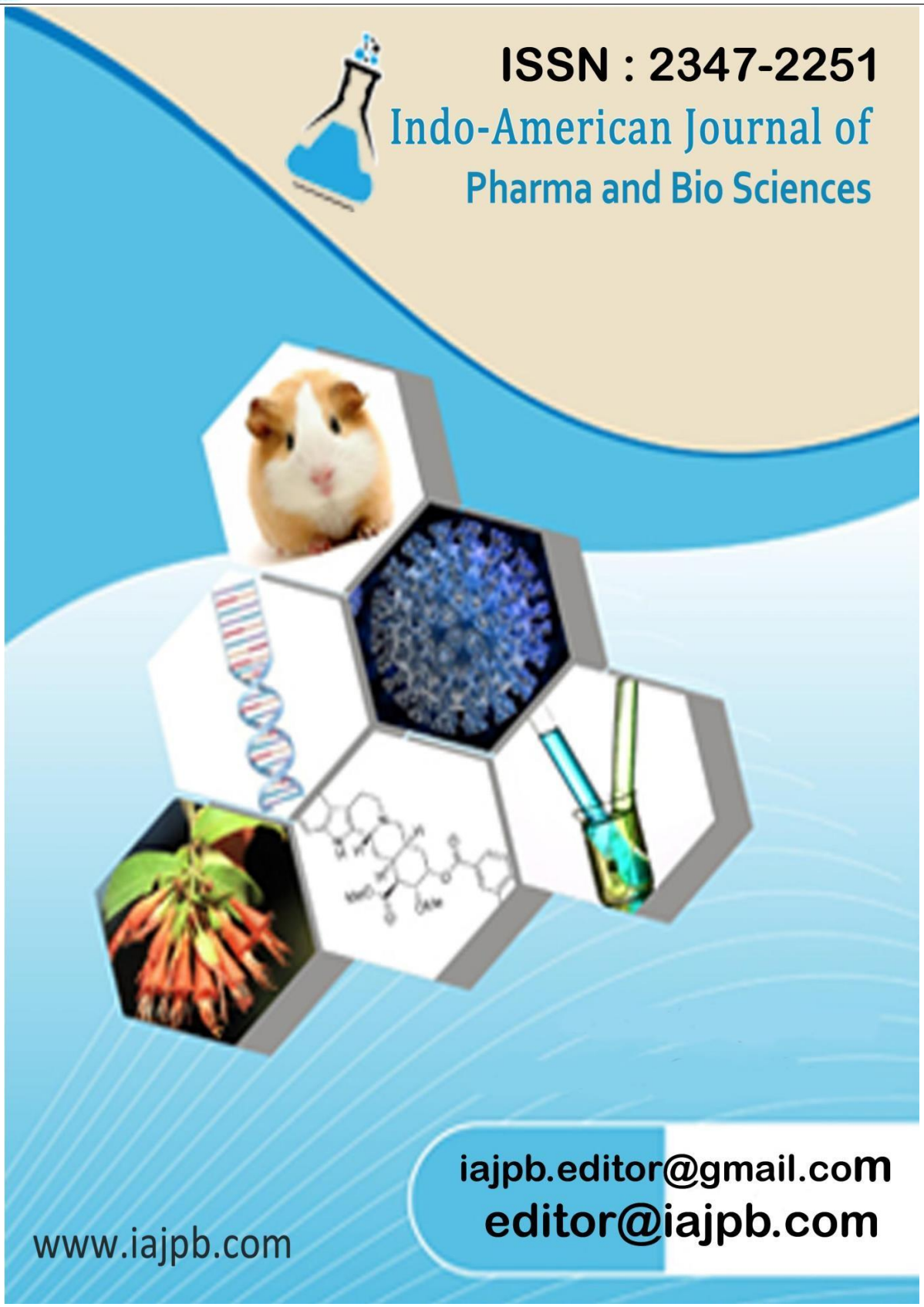
Indo-American Journal of Pharma and Bio Sciences

Vol. 20, Issuse 4, Nov 2022



Indo-American Journal of Pharma and Bio Sciences

Vol. 20, Issuse 4, Nov 2022

FORMULATION AND EVALUATION OF APIXABAN ORIDISPERSIBLE FAST DISSOLVING TABLETS

M.SHIREESHA, *Dr.V. PRABHAKAR Reddy*

Article Info

Received: 19-08-202 *Revised:10 -09-2022* *Accepted: 02-10-2022*

ABSTRACT

Different Apixaban tablets were prepared by incorporating various excipients, such as PEG 600 by melting method PEG is used as a lubricant, microcrystalline cellulose as a diluent, sodium starch glycolate as a capsule disintegrant, mannitol as a sweetening agent, and magnesium as a capsule lubricant. The work was done to improve the dissolution properties of the practically insoluble anticoagulant drug Apixaban. It was determined that post-compressional criteria such weight fluctuation, hardness, friability, drug content, and in vitro dissolving experiments were all favourable for the development of Apixaban tablets. Research using Fourier transform infrared spectroscopy (FTIR) indicated no chemical interaction between the medication and excipients. These findings highlight a key advantage of Apixaban tablets over directly compressed ones: a higher percentage of drug release due to their superior wetting qualities and larger surface area for drug disintegration. This research shows that the solid dispersion approach is a viable option for increasing the water solubility of medications that are otherwise difficult to dissolve in water.

Introduction

Forms of Solid Dosage

Medications are most often given orally since it is the most practical way to achieve both local and systemic effects. Parenteral, oral, buccal, transdermal, nasal, and pulmonary routes of administration may all be used to bring about systemic distribution of a medication. The physiological parameters for an "optimal" absorption location are too varied to be met by a single pathway. However, the oral route has more favourable properties for drug absorption due to its surface area, low metabolic activity, contact duration, blood supply, accessibility, lack of variability, and permeability. It is generally accepted that oral dose forms are the most suitable way of medication administration. Patients are used to receiving medications orally and prefer this procedure since it is less intrusive.

Branch : Pharmaceutical

Pharmaceutical Data analysis

Clog :Palamuru University College of Pharmaceutical Sciences

Indo-American Journal of Pharma and Bio Sciences

Vol. 20, Issuse 4, Nov 2022

Tablets, capsules, and granules continue to be the dosage form of choice in today's modern medicine, with the oral route accounting for an estimated 80% of all pharmaceuticals taken. So, it's crucial that research into oral medication delivery methods keeps progressing so that treatments are even more secure and effective. The overwhelming majority of the medication delivery industry is comprised of oral dosage forms due to its many advantages over other routes of administration, including greater safety, greater effectiveness, lower costs, and more customer compliance. There are substantial regulatory, technological, and compliance challenges to the cost-effective use of the transdermal, injectable, and inhalable routes to a broad variety of chemicals. Most of the time, the dosage and timing of the medicine's absorption and distribution is completely out of the hands of the patient using the standard oral drug delivery method. Drug concentrations at the site of action may be maintained at an optimal level by delivering massively excessive dosages on an as-needed basis. If a drug has poor membrane permeability, its permeation rate will be unpredictable, and its plasma concentration will be either below or above therapeutic levels, causing severe side effects. However, effective concentration at the target site can be achieved through intermittent administration of grossly excessive doses.

Table.No.:1. Different components of GIT and its drug action.

Code	Area	Property
A	Oral	pH 6.8. small surface area, lipophilic, neutral and basic drugs absorbed directly into the systemic circulation.
B	Stomach	pH 1-3. not too large surface area, lipophilic, neutral and acidic drugs absorbed but lesser than that from intestine
C	Small Intestine	pH 5-7.5. very large surface area, major site for absorption of all types of drugs (lipophilic, neutral, acidic or basic drugs)
D	Colon	pH 7.9-8. small surface area, all types of drugs are absorbed but to a lesser extent

TABLETS Tablet is defined as a compressed solid dosage form containing medicaments with or without excipients.

Tablets are defined as "unit dosage forms" in the Indian Pharmacopoeia, and are made by compressing a medication or drug combination, with or without diluents, into a solid, flat or biconvex dish. Depending on the quantity of active ingredients and the route of administration, they have many different forms and range widely in size and weight. Seventy percent of all drugs are distributed in tablet form, making it the most common dosage type. Low water solubility and/or poor membrane permeability of the drug molecule are two of the most critical variables that restrict medication absorption in the gastrointestinal (GI) tract. When administered orally, the active drug must first dissolve in stomach and/or intestinal fluids before it can pass through the GI tract's membranes and into the body's circulatory system. Since poor water solubility is correlated with a slow dissolving rate and poor absorption, it stands to reason that such a medicine would be similarly ineffective. Therefore, improving the solubility and dissolution rate of poorly water-soluble medications and boosting the permeability of weakly permeable pharmaceuticals are two areas of pharmaceutical research focused on increasing the oral bioavailability of active molecules. In this context, the application of solid dispersion technologies to enhance the oral bioavailability of weakly water-soluble medicines is of special interest. Because of the various benefits associated with this route, including increased stability, decreased weight, precise dosing, and simple manufacture, the vast majority of NCEs now under development are designed to be taken orally. When it comes to bioavailability, oral distribution of NCEs is often linked with low bioavailability, considerable intra- and inter-subject variability, and a lack of dosage proportionality since most NCEs are poorly water-soluble medicines that are not well-absorbed after oral administration.

It is predicted that 40 percent of the newly found chemical entities are not very soluble in water. Methods such as prodrug formation, complexation, microencapsulation, the addition of surfactants,

Indo-American Journal of Pharma and Bio Sciences

Vol. 20, Issuse 4, Nov 2022

lipids, permeation enhancers, micritization, salt formation, cyclodextrins, nanoparticles, solid dispersions, and a self-emulsifying drug delivery system have all been used to address the issues of oral absorption and bioavailability. A solid dispersion formulation strategy has been found to considerably improve medication absorption. The phrase "solid dispersion" is used to describe a class of solid goods with at least two distinct elements, often a hydrophilic matrix and a hydrophobic medication. Crystalline or amorphous, the matrix may take any form. The medication is released as colloidal particles when the solid dispersion is brought into contact with water. A greater dissolution rate and improved bioavailability of weakly water-soluble medicines are the results of this increased surface area. Moreover, in solid dispersions, some of the medication dissolves instantly to saturate the GI tract fluid, while the remainder precipitates as tiny colloidal particles or oily globules of submicron size. Figure 1 is a simplified illustration of the benefit of solid dispersions over the more traditional tablet or capsule.

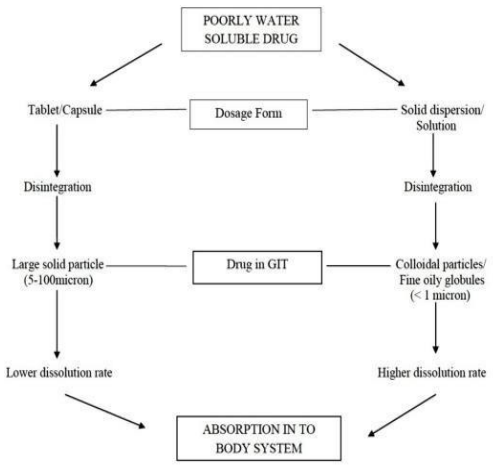


Figure 1: A schematic representation of the bioavailability enhancement of a poorly water- soluble drug by solid dispersion compared with conventional tablet or capsule

Solid dispersion

Solid dispersion technology is the science of dispersing one or more active ingredients in an inert matrix in the solid stage to achieve an increased dissolution rate or sustained release of drug, altered solid state properties and improved stability.

CARRIERS OF SOLID DISPERSION

Poly ethylene glycol (PEG)

Poly ethylene glycols (PEG) are polymers of ethylene oxide, with a molecular weight usually falling in the range 200-300000. For the manufacture of solid dispersions and solutions, pegs with molecular weights of 1500-2000 are

Indo-American Journal of Pharma and Bio Sciences

Vol. 20, Issuse 4, Nov 2022

usually employed. As the molecular weight rises, so does the viscosity of the PEG. At molecular weight of up to 600, PEGs are fluid, in the range 800 -1500 they have a consistency that is best described as Vaseline-like, from 2000 to 6000 they are waxy and those with molecular weight of 20 000 and above form hard, brittle crystals at room temperature. Their solubility in water is generally good, but reduces with molecular weight. A meticulous advantage of PEGs for the solid dispersions is that they have good solubility in numerous organic solvents. The melting point of the PEGs of interest lies under 650C in every case (e.g., the m.p. of PEG 1000 is 30- 400C, the m. p of PEG 4000 is 50-588C and the m.p. of PEG 20 000 is 60-630C).

Poly vinyl pyrrolidone (PVP)

Polymerization of vinylpyrrolidone leads to polyvinylpyrrolidone (PVP) of molecular weights ranging from 2500 to 3000 000. These can be classified according to the K value, which is calculated using Friendster's equation13. The temperature of a given PVP is dependent not only on its molecular weight but also on the moisture content. In general, the glass transition temperature (Tg) is high; for example, PVP K25 has a Tg of 1558C. For this reason, PVPs have only restricted application for the preparation of solid dispersions by the hot melt method. Due to their excellent solubility in an ample variety of organic solvents, they are mostly suitable for the preparation of solid dispersions by the solvent method. Improved wetting and thereby an improved dissolution rate from a solid dispersion in PVP has been demonstrated for fufenamic acid.

Cellulose Derivatives

Hydroxy propyl methyl cellulose (HMPC) Hydroxy propyl methyl cellulose are mixed ethers of cellulose, in which 16.5-30% of the hydroxyl groups are methylated and 4-32% are derivatized with hydroxypropyl groups. For example, Type 2910 has an average methoxy content of 29% and an hydroxypropyl content of 10%. The molecular weight of the Hydroxy propyl methyl cellulose ranges from about 10,000 to 1,50,0000 and they aresoluble in water and mixtures of ethanol with dichloromethane and methanol with dichloromethane.

Hydroxy propyl cellulose (HPC)

Hydroxy propyl cellulose (HPC) exhibits good solubility in a range of solvents, including water (up till 400C), ethanol, methanol and chloroform. The average of the molecular weight HPCs ranges from 37 000 (Type SSL) to 11,50,000 (Type H).

Carboxy methyl ethyl cellulose (CMEC)

Indo-American Journal of Pharma and Bio Sciences

Vol. 20, Issuse 4, Nov 2022

Carboxy methyl ethyl cellulose also belongs to the cellulose ethers, but unlike many of the others it is resistant to dissolution under gastric (acidic) conditions. It dissolves readily at Ph values above 5-6, with lowest dissolve union Ph being dependent on the grade of the Carboxy methyl ethyl cellulose. Carboxy methyl ethyl cellulose also dissolves readily in acetone, isopropanol 70%, ethanol 60% and 1:1 mixture of dichloromethane and ethanol. Amorphous solid dispersions of nifedipine and spironolactone show enormous increases in the dissolution rate of the drug at PH values of 6.8.

Hydroxy propyl methyl cellulose phthalate (HPMCP)

Hydroxy propyl methyl cellulose phthalate are cellulose esters which are often used as enteric coatings. Depending on the grade, they dissolve first at pH 5 (HP 50) or pH 5.5 (HP 55). They are having a type-dependent solubility in organic solvents. Their molecular weight ranges from 20,000 to 2000,000. The dissolution rate of griseofulvin at pH 6.8 could be greatly enhanced by incorporating it in a evaporate of Hydroxy propyl methyl cellulose phthalate. Using a spray drying technique to form a solid dispersion in HP 55, the dissolution rate of the anti-fungal drug MFB-1041 could be increased by a factor of 12.5 as compared to the best possible dissolution achievable by micronizing the drug.

Polyacrylates and polymethacrylates

Polyacrylates and polymethacrylates are glassy substances that are produced by the polymerization of acrylic and methacrylic acid, and derivatives of these polymers such as esters amides and nitriles. In pharmaceuticals they are mainly used as coatings to change the release of the drug from the dosage form. Commonly they are referred to by the trade name Eudragit drug18. On the other hand, Eudragit L has been successfully used to increase the dissolution of griseofulvin and spironolactone at a pH value of 6.8.

Urea

Urea is the end product of human protein metabolism, has a light diuretic effect and is regarded as non-toxic. Its solubility in water is greater than 1 and it also reveals good solubility in several common organic solvents. In one of the first bioavailability studies of solid dispersions, it was shown that sulphathiazole was better absorbed in rabbits when given as eutectic with urea.

METHODS OF PREPARATION OF SOLID DISPERSIONS:

Fusion method

The fusion method is sometime referred to as the melting method only if the starting material is crystalline. In this method, the carrier is heated to a temperature just above its melting point and the drug is incorporated in to the matrix. The mixture is cooled with constant stirring in order to obtain homogeneously disperse matrix. The first dispersion of sulfathiazole and urea was prepared by fusion method, by melting at the eutectic composition followed by cooling step. The eutectic composition was chosen to obtain simultaneous crystallization of drug and matrix during cooling. Polymers like Polyethylene glycols and Poly vinyl pyrrolidone, are mostly used in this method.

Limitations:

This method is not suitable if the carrier is high-melting solid and the drug is heat sensitive. Sometime may be a problem during cooling stage when the drug-matrix miscibility changes which may produce phase separation.

Hot melt extrusion method:

This method is same as fusion method except that the intensive mixing is induced by the extruder. The twin-screw extruder or single-screw extruder is used in this method. This method offers the potential to shape the heated mixture in to implants, implants insert, oral dosage forms. To predict the solid-state solubility and to select matrix suitable for melt extrusion, the solubility parameters are investigated. High shear forces resulting in high temperature in extruder may create a problem for heat sensitive materials. The main advantage is the handling of product is easier because at the outlet of the extruder the shape can be adapted to the next processing step without grinding. The polymers like Hydroxypropyl cellulose, Hydroxypropyl cellulose phthalate, Eudragit, Cellulose acetate phthalate (CAP), Poly vinyl alcohol (PVA), and Hydroxypropyl cellulose (HPC) can be used. Laing Wang, et al., have prepared solid dispersion of Nitrendipine with silica particles using the melt mixing method. Solvent evaporation method in this method, the carrier and the active ingredients are dissolved in suitable organic solvent. The second step involves the removal of solvent(s) under vacuumed (sometime heat may be applicable with vacuumed). When the solvent evaporates, super saturation may occur followed by simultaneous precipitation of the constituents resulting in a solid residue.

During formulation, the formulation scientist has to face two challenges;

It is difficult to mix drug and polymer in one solution having different polarity.

Indo-American Journal of Pharma and Bio Sciences

Vol. 20, Issuse 4, Nov 2022

It is difficult to prevent phase separation during removal of solvent(s).

The recovery of solvent from coprecipitate takes longer time

Example:

Ethanol: -5°C and reduced pressure followed by drying for 12 h in vacuum Methanol/Chloroform: 115°C for 1 hour or 125°C for 25 min from Griseofulvin- PEG 6000 dispersion. Drying at high temperature speeds up the drying process and reduces the time available for phase separation. On the other hand, high temperature speeds up the phase separation (example: crystallization) because of the increase in the mobility of drug and polymer. Sometime solvent evaporation could be increased by using rotary evaporator followed by storing the residue in a vacuum desiccator to remove the residual solvent. Sometime vacuum drying at elevated temperature may cause phase separation because the mobility of drug and matrix decreases slowly. The freeze-drying method can be used to evaporate the solvent hence the solvent should have high melting point and high vapor pressure. For example: Dimethyl sulfoxide (DMSO) has high melting point (1900C) but it has very low vapor pressure (0.08 kPa) hence not suitable solvent, but 2-methyl-2- propanol or tertiary butanol (TBA) is suitable solvent because it has high melting point (125° C) and vapor pressure (5.49 kPa).

Advantages:

Minimal thermal stress during preparation.

Reduction in chances of phase separation.

Characterization of Solid Dispersion

Many methods are available that can contribute information regarding the physical nature of solid dispersion system.

A combination of two or more methods is required to study its complete picture.

- Thermal analysis.
- X-ray diffraction method.
- Spectroscopic method.
- Modulated temperature differential scanning calorimetry.
- Environmental scanning electron microscopy
- Dissolution testing.
- Laboratory tests of dissolving in vitro.

Processes for Analysing Temperature:

During thermal analysis, a material is put to a controlled temperature programme so that its physical properties may be measured as a function of temperature. Differences in temperature between a sample and a reference material heated to the same temperature are determined using differential thermal analysis. Differential scanning calorimetry, a similar method, uses the disparities in the amount of energy needed to keep the sample and the reference at the same temperature. Dilatometry detects the length or volume changes that occur in materials during heat treatment; X-ray or neutron diffraction may also be employed for this purpose. Samples that degrade at high temperatures are required for both thermogravimetry and evolved gas analyses. The first method keeps tabs on the sample's mass as it heats, whereas the second relies on the gases released when the sample is heated. Changes in the defect density of materials or phase transitions may be studied in relation to electrical conductivity measurements.

Crystallography by Use of X-Rays

The structure of a substance may be analysed with the use of X-ray crystallography.

crystal, whereby an X-ray beam is directed towards the crystal and diffracted in several different directions upon impact. It is possible for a crystallographer to construct a three-dimensional image of the electron density inside the crystal by measuring the angles and intensities of these diffracted beams. The average atomic locations, chemical bonds, and even the degree of disorder in a crystal may all be deduced from its electron density. Given that many materials may form well as diverse inorganic, organic, and biological compounds. The use of X-ray crystallography has been crucial to the growth of several scientific disciplines. During its first several decades of use, this technique was used to measure atomic size, chemical bond length and type, and identify minute variations in composition across a wide range of materials, including minerals and alloys. Spectroscopy was at first defined as the study of the wavelength-dependent () interaction between radiation and matter. Historically, spectroscopy meant the use of visible light that has been separated into its component wavelengths, such as by the use of a prism. Subsequently, the scope of the idea broadened considerably to include any number that could be measured in terms of wavelength or frequency. Calorimetry using a temperature-dependent modulation scheme (MDSC).

Spray-dried samples and input components were tested three times. For MDSC measurements, a DSC with a cooling refrigerator is used. Purification of the DSC cell was accomplished using a flow of dry nitrogen set at 50 ml/min. All measurements were made in open metal pans.

Indo-American Journal of Pharma and Bio Sciences

Vol. 20, Issuse 4, Nov 2022

When figuring out how much heat was being transferred, we included in the weight of both the sample and reference containers. The size of the samples ranged from 1 to 6 mg. Standard indium was used to calibrate the enthalpic response, while octadecane, indium, and tin were used to calibrate the temperature scale. Using the response of a sapphire disc and the corresponding value from the literature at 80 degrees Celsius, we were able to calibrate the heat capacity signal. Scanning Electron Microscopy in the Environment:

Spray-dried ternary solid dispersions may be defined by their shape using

The microscope is an environmental scanning electron microscope (ESEM) of the Philips XL30 kind, equipped with a FEG field emission gun, and working at 25 kV accelerating voltage in a vacuum. Samples were sprayed onto double-sided carbon tape and attached to standard SEM stubs for examination.

Dissolution Evaluations Dissolution

There is enough room in the binary and ternary distributions for three sets of experimentation. All of the tests were conducted using a Hanson SR8plus dissolving device and the USP 24 method 2. Dissolving of a weak basic chemical was mimicked by using 500 mL of pepsin-free gastric juice at 37 °C and 100 rpm as a dissolution medium. The dissolving media was supplemented with a quantity of the spray-dried powders equal to a drug dosage of 100 mg. A five-millilitre sample was obtained at 5, 10, 15, 30, 45, 60, and 120 minutes, and then immediately replaced with new dissolving medium. We used 0.45-micron Teflon filters on these samples. There was a waste of the first 2 ml. Precipitation was avoided by diluting the rest with methanol (1/2) before HPLC analysis.

In-vitro Research on Solubility In-vitro

studies of dissolution are conducted to learn about dissolution characteristics. Using in-vitro dissolution studies in vivo correlation, a drug's bioavailability or bioequivalence may be shown (IVIVC). If, on the other hand, absorption is dissolution rate restricted, the medication diffuses freely through the bio-membranes into the gastrointestinal fluid at a rate greater than the rate at which the dosage form dissolves or releases its contents. In a solid dispersion system, the absorption rate, and therefore its bioavailability and final bioequivalence, can only be determined by a well-planned in-vivo dissolving research.

ADVANTAGES AND DISADVANTAGES

Advantages of Solid Dispersions:

- Improving drug bioavailability by changing their water solubility has been possible by solid dispersion.
- Solid dispersions are more efficient than these particle size reduction techniques, since the latter have a particle size reduction limit around 2- 5 mm which frequently is not enough to improve considerably the drug solubility or drug release in the small
- intestine.
- Increase in dissolution rate & extent of absorption and reduction in Pre systemic metabolism.
- Transformation of liquid form of drug into solid form.
- Parameters, such as carrier molecular
- weight and composition, drug crystalline and particle porosity and wettability, when successfully controlled, can produce improvements in bioavailability39.

Disadvantages of Solid Dispersions:

- Most of the polymers used in solid dispersions can absorb moisture, which may result in phase separation, crystal growth or conversion from the amorphous to the crystalline state or from a metastable crystalline form to a more stable structure during storage. This may result in decreased solubility and dissolution rate.
- Drawback of solid dispersions is their poor scale-up for the purposes of manufacturing.

Applications of Solid Dispersions

Apart from absorption enhancement, the solid dispersion technique may have numerous pharmaceutical applications, which should be further explored.

It is possible that such a technique be used:

- ❖ To obtain a homogeneous distribution of a small amount of drug in solid state.
- ❖ To stabilize the unstable drug.
- ❖ To dispense liquid or gaseous compounds in a solid dosage.
- ❖ To formulate a fast release primary dose in a sustained released dosage form.
- ❖ To formulate sustained release regimen of soluble drugs by using poorly soluble or insoluble carriers.
- ❖ To reduce pre systemic inactivation of drugs like morphine and progesterone. Polymorphs in a given system can be converted into isomorphism, solid

Indo-American Journal of Pharma and Bio Sciences

Vol. 20, Issuse 4, Nov 2022

solution, eutectic or molecular compounds.

- To increase the solubility of poorly soluble drugs thereby increase the dissolution rate, absorption and bioavailability.
- To stabilize unstable drugs against hydrolysis, oxidation, recrimination, isomerisation, photo oxidation and other decomposition procedures.
- To reduce side effect of certain drugs.
- Masking of unpleasant taste and smell of drugs.
- Improvement of drug release from ointment, creams and gels.
- To avoid undesirable incompatibilities.
- To obtain a homogeneous distribution of a small amount of drug in solid state.
- To dispense liquid (up to 10%) or gaseous compounds in a solid dosage.
- To formulate a fast release primary dose in a sustained released dosage form.

LITERATURE REVIEW

Authors Yangban Huang et al (2019)

analysed the basics of using solid dispersion technology to provide medications with limited solubility. A drug's release rate is regulated by the matrix. For medications that don't dissolve well in water, solid dispersion has shown to be an effective method of solubilization. A solid dispersion is a drug-polymer two-component system, thus the interaction between the two is crucial to its development and effectiveness. Here, we highlight the basic characteristics of this crucial technology by summarising our present knowledge of solid dispersions in both the solid state and in dissolution.

Among those who have contributed to this field are Nisar Ahmed Khan (2018)

researched the technology of solid dispersion at a high level. This research set out to investigate Approximately 40% of NCEs discovered by the pharmaceutical industry today via combinatorial chemistry and high through put screening are highly lipophilic or poorly water-soluble compounds. This dramatic increase in the number of such compounds has made the solubility behaviour of these drugs one of the most challenging aspects in formulation development. Solid dispersions have emerged as an advanced technique of improving the solubility/dissolution rate and consequently, the bioavailability enhancement of a wide range of poorly water-soluble drugs, joining the ranks of the many strategies (such as particle size reduction, use of surfactants, solvency, hydro trophy, etc.) already reported in the literature to resolve this issue. The categorization, kinds, benefits, limits, methods of production, and characterisation of solid dispersions are discussed in detail, as well as the solubility ranges, biopharmaceutical classification system (BCS), list of poorly soluble pharmaceuticals, commercial preparations, and so on. In addition to the aforementioned, the goals of this study are to talk about the new developments and potential of the solid dispersion technology.

Authors Sameer Singh et al (2018)

substance dispersion was evaluated. As a practical strategy for increasing the bioavailability of a wide variety of medications that are poorly water-soluble, solid dispersions have garnered a lot of attention. Fortunately, these issues have been mitigated and dissolution improved by the use of solid dispersions of weakly water-soluble medicines with water-soluble carriers. In this post, we'll look at the benefits, drawbacks, and preparation and characterisation techniques for solid dispersion.

brusquer, OG., et al (2017)

analysed on Nearly 40% of NCEs are medications that aren't very good at dissolving in water. As the rate-limiting phase in the digestive tract absorption of medications, solubility behaviour of the pharmaceuticals remains one of the most problematic factors in formulation development. Because of this, valuable goods never make it to market or never realise their full potential. There has been a lot of focus on solid dispersion as a viable strategy for increasing the solubility and bioavailability of hydrophobic pharmaceuticals. In this essay, we will go over the basics of solid dispersion, including its mechanism, optimal candidates, categorization, manufacturing method, carrier selection, characterisation, and restrictions.

It was Anshul Sharma and company (2011)

analysed on Increased medication solubility in water by solid dispersion is an exciting new development. Compounds with low water solubility have difficulties with dissolution and bioavailability. This article offers a comprehensive discussion of laboratory and industrial methods for producing solid dispersion technology. It is important to know about the different hydrophilic polymers that are utilised in this method to improve the solubility of medications that are not easily soluble. A discussion of contemporary methods for characterising solid dispersion is included. The goal of this article is to talk about new developments in the field of solid dispersion technology.

Indo-American Journal of Pharma and Bio Sciences

Vol. 20, Issuse 4, Nov 2022

Authors Qing Hou et al (2018)

intended for Maximizing Ginkgolide B Solid Dispersion Efficiency. The primary goal of this research is to enhance the solubility of Ginkgolide B (GB) in water by modifying the formulation of GB solid dispersion. We use the solvent technique to create the GB solid dispersion. The ideal formulation includes PVPK30 as the carrier, ethanol: dichloromethane = 1:1, and GB at a concentration of 1:10 in PVPK30. For 10 minutes at 60 degrees Celsius, they were subjected to ultrasonic treatment. The morphological appearance of GB altered dramatically in solid dispersion, as shown by the findings of scanning electron microscopy (SEM), differential scanning calorimetry (DSC), X-ray diffraction (XRD), and particle size analysis. GB had lost its crystalline structure and instead was found to be non-uniformly scattered throughout PVPK30. This is likely due to the formation of hydrogen bonds between the -C=O groups in GB and the -OH groups in PVPK30 or urea, which results in a good solid dispersion and greatly enhances GB's solubility in water. It has been estimated that the dissolution rate of GB in water might increase by as much as 80% when GB is included in a solid dispersion system. In addition, it may theoretically be manufactured as a solid agent.

Dr. Tomoka Takatani-Nakase, Dr. (2016)

Formulated Wet Granulation Method for Preparation of Solid Dispersion Tablets Using Porous Calcium Silicate: Evaluation of Preparation and Manufacturing Efficacy. In this research, porous calcium silicate (PCS) was used in a wet granulation process to create solid dispersion tablets containing a weakly water- soluble medication. As a prototypical weakly water-soluble medication, nifedipine (NIF) served as the experimental subject. Tablets for solid dispersion were made utilising a high-speed mixer granulator and ethanol and water for the wet granulation process. Seven and four candidates for the binder and disintegrant, respectively, were ultimately chosen. The JP 16 paddle technique was used for the dissolving test. Animals were fasted to examine NIF absorption after oral administration. The two ingredients chosen for these roles are xylitol and crospovidone. When compared to NIF powder and physical blends, NIF dissolve rates were significantly increased when using solid dispersion formulations. NIF's decreased crystallinity in the solid dispersion formulations was verified by powder X-ray diffraction (PXRD). The physical interaction of NIF and PCS in the solid dispersion formulations was shown by Fourier transform infrared (FT-IR). It is the amorphous form of NIF that is found in granules made by the wet granulation process, which employs the use of water. Dosing rats with the solid dispersion granules resulted in higher plasma NIF AUC and Cmax values compared to dosing with NIF powder. The dissolution rates and oral bioavailability of NIF solid dispersion formulations created with PCS utilising the wet granulation process were much higher than those of the parent drug. This approach is quite straightforward, and it has the potential to be used in the creation of additional medications that have low solubility in water.

MATERIALS AND EQUIPMENTS

List of Materials and their applications in Formulation

DRUG PROFILE

S.No	Name of the materials	Manufacturer / Supplier
1.	Apixaban	Apex Laboratories
2.	PEG 6000	Nice
3.	Microcrystalline Cellulose PH 102 (Avicel 102)	Accent Industries
4.	Croscarmellose sodium	Accent Industries

Equipment used for formulation:

Sr. No.	NAME OF INSTRUMENT	MANUFACTURING COMPANY
1.	Digital Balance	Shimadzu Corporation, AW220 &BX6205
2.	Tablet hardness tester	Pfizer hardness tester
3.	Friability tester	Roche Fribilator
4.	Vernier Caliper	Mitutoyo digimatic caliper
5.	Disintegration apparatus	Rolex
6.	Dissolution apparatus USP	Electrolab tablet dissolution apparatus
7.	Double beam UV Spectrophotometer	Lab India UV 3000
8.	Rotary tablet punching machine	Proton Mini press
9.	pH meter	Systonic 335

Indo-American Journal of Pharma and Bio Sciences

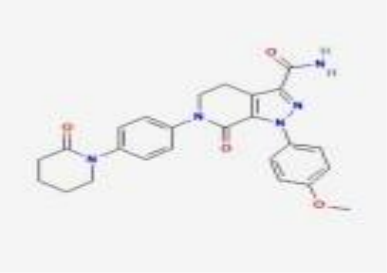
Vol. 20, Issuse 4, Nov 2022

Apixaban is an anticoagulant and the first orally active direct factor Xa inhibitor. Unlike warfarin, routine lab monitoring of INR is not necessary. However, there is no antidote available in the event of a major bleed. Only the 10 mg tablet can be taken without regard to food. The 15 mg and 20 mg tablet should be taken with food. FDA approved on July 1, 2011. Specifically, it is used to treat deep vein thrombosis and pulmonary emboli and prevent blood clots in atrial fibrillation and following hip or knee surgery. Apixaban was patented in 2007 and approved for medical use in the United States in 2011. In the United States, it will not be available as a generic medication until 2024.

IUPAC Name:

1-(4-methoxyphenyl)-7-oxo-6-[4-(2-oxopiperidin-1-yl) phenyl]-4,5-dihydropyrazolo[3,4-c] pyridine-3-carboxamide.

Structure:



CAS No.: 366789-02-8.
Molecular Weight: 435.9 g/mol.
Molecular formula: $C_{25}H_{25}N_5O_4$

Properties:

Description:

Apixaban is a pure (S)-enantiomer. The powder ranges in colour from white to yellow and lacks odour and hygroscopicity.

Solubility:

Apixaban is very marginally soluble in organic solvents (e.g., acetone, polyethylene glycol 400) and is completely insoluble in water and aqueous solutions.

Melting point: 230°C.

Storage: Store in well-closed container.

Indication: Coagulation factor X

Apixaban's FDA-approved uses include the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) and the reduction of the risk of recurrent DVT and/or PE, as well as the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. Patients with chronic coronary artery disease or peripheral artery disease may benefit from using apixaban in conjunction with aspirin to lessen their risk of serious cardiovascular events. No research has been done on its safety; hence it shouldn't be given to minors. The same goes for those with severe renal impairment, for whom its usage is not suggested.

Dosage & Administration

Apixaban 2.5mg, 10mg, 15mg, 20mg available as pills.

Deep Vein Thrombosis Prophylaxis for Hip or Knee Replacement Surgery

Start 6-10 hours after surgery after hemostasis has been achieved Knee replacement: 10 mg PO qDay for 12 days Hip replacement: 10 mg PO qDay for 35 days.

Venous Thromboembolism Prophylaxis and Restricted Mobility

10 mg PO qDay, in inpatient and after hospital release, for 31-39 days

Nonvalvular Atrial Fibrillation

20 mg PO qDay

Deep Vein Thrombosis and/or Pulmonary Embolism Treatment

15 mg PO q12hr for 21 days, THEN 20 mg PO qDay Indicated for decrease in risk of recurrence of DVT and/or PE in patients at ongoing risk for recurrent DVT and/or PE after completion of first therapy lasting at least 6 months 10 mg PO qDay, following at least 6 months of regular anticoagulant therapy

Deflection of Potentially Catastrophic Cardiovascular Events

Indo-American Journal of Pharma and Bio Sciences

Vol. 20, Issuse 4, Nov 2022

Those with chronic CAD or PAD should take 2.5 mg PO BID in addition to aspirin (75-100 mg qDay) to lower their risk of significant cardiovascular events such CV mortality, MI, and stroke.

To what extent is absorption a factor in pharmacokinetics?

After being taken orally, Apixaban is quickly absorbed and achieves its maximum plasma concentration in within two to four hours. A 10 milligramme dosage has a bioavailability of more than 80 percent. The 15-20 mg dosage, however, has decreased absorption when taken in the fasting condition and hence is best consumed with meals.

In a steady state distribution, Vd is 50 L. Between 92% and 95% of plasma proteins are bound.

Metabolism:

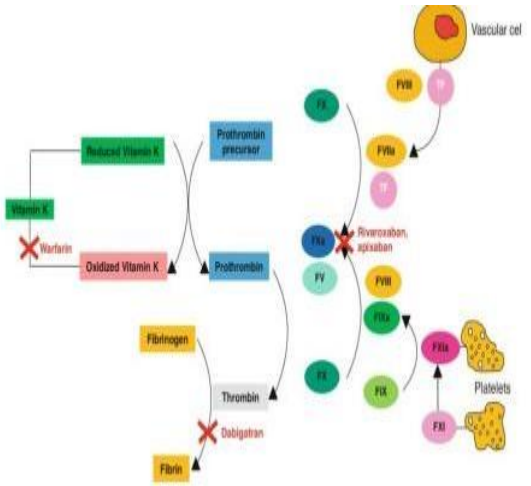
About two-thirds of the dosage gets broken down into usable forms. CYP3A4, CYP3A5, CYP2J2, and CYP-independent pathways all contribute to its metabolism.

Excretion:

Approximately 36% of Apixaban is eliminated into urine unaltered, whereas the remaining 70% undergoes inactive metabolism. In the faeces, the remaining third of the dosage is broken down into 7% unaltered medication and 21% inactive metabolites. Adults have a terminal half-life of 5-9 hours, whereas the elderly have a half-life of 11-13 hours. Apixaban is a medication with limited clearance since its systemic clearance is only around 10 L/h. There is a clearance of about 3-4 litres per hour in the kidneys.

what the mechanism of action is.

Vildagliptin's Mode of Action



Apixaban suppresses both free and clot-bound factor Xa via a competitive mechanism. In order to convert prothrombin (factor II) to thrombin, factor Xa must first be present (factor IIa). To complete the clotting process, fibrinogen must be activated into fibrin, a loose meshwork. Thrombin, a serine protease, is necessary for this to happen. Selective inhibitors of factor Xa are very beneficial since only one molecule of factor Xa may produce over a thousand times that amount of thrombin. Apixaban has a permanent effect on the body.

Negative Consequences:

Hematoma, Back Pain, Wound Secretion, Abdominal Pain, Dizziness, and Pruritus are the Most Frequently Reported Adverse Effects in Patients Receiving Apixaban. Extremity pain, Disorders such as insomnia, anxiety, blisters, fatigue, muscles spasms, syncope, major bleeding, atrial fibrillation, deep vein thrombosis prevention, deep vein thrombosis therapy, and venous thromboembolism prevention.

Hypersensitivity Patients with active pathological bleeding Patients who have undergone transcatheter aortic valve replacement

The Process of Formulation Development

1. Dissemination of solids, prior to preparation

2. To make a solid dispersion, the carrier is melted first. Distributed solids (SDs)

3. Apixaban in PEG6000 solutions of several weight ratios (1:1, 1:2, 1:3, 1:4, and 1:5) were created through melting. The melted PEG 6000 was mixed with the apixaban at 75 degrees Celsius, and the resultant homogeneous preparation was quickly chilled in a freezing combination of ice and sodium chloride before being kept in desiccators for 24 hours. The mixture was then mortared and sieved through a 50# mesh.

Combine Physically Co-mingling in a physical sense (PMs)

Apixaban and PEG 6000 were mixed well in a mortar to achieve a homogeneous mixture with the desired weight ratios. The powdered mixture (PM) was obtained after passing it through a 50# sieve.

To make a solid dispersion, the carrier is melted first.

Indo-American Journal of Pharma and Bio Sciences

Vol. 20, Issuse 4, Nov 2022

Formulation code	Drug	Carrier	Drug:Carrier ratio	Method
SD1	Apixaban	PEG 6000	1:1	Melting method
SD2	Apixaban	PEG 6000	1:2	
SD3	Apixaban	PEG 6000	1:3	
SD4	Apixaban	PEG 6000	1:4	
SD5	Apixaban	PEG 6000	1:5	
PM1	Apixaban	PEG 6000	1:1	Mixing in mortar & Pestle
PM2	Apixaban	PEG 6000	1:2	
PM3	Apixaban	PEG 6000	1:3	
PM4	Apixaban	PEG 6000	1:4	
PM5	Apixaban	PEG 6000	1:5	

Characterization of solid dispersions of Apixaban:

Medicamentous material

Each solid dispersion and physical mixture's drug content was calculated using UV spectroscopy. To dissolve 2 mg of Apixaban, a weighed amount of the solid dispersion or physical combination was added to 10 ml of methanol in a 100 mL volumetric flask. 0.1 N HCL was added to get the volume up to 100 ml. A 0.45-mm membrane filter paper was used to purify the solution. The absorbance at 282 nm was determined by diluting one millilitre of this solution one hundred times with 0.1 N HCL.

Analysis of Solubility Phases

Overloads of medication (20 mg) were added to screw-capped vials holding 20 ml of aqueous solution of varying PEG 6000 concentrations for phase-solubility assays. The suspensions were swirled at 250 and 370 degrees Celsius and 300 revolutions per minute on an electromagnetic stirrer for three days (this duration was previously tested to be sufficient to reach equilibrium). To remove the particles from the suspensions, a 0.22 m membrane filter was used. The filtrate was diluted appropriately, and the dissolved drug was detected using spectrophotometry at 248 nm.

Research on Solubility

The dissolution of powdered Apixaban, SDs, and PMs were studied using a USP type II paddle device at a paddle rotation of 75 rpm and a dissolving medium of 900 cc of Acetate buffer pH 4.5 (with 0.4% of sodiumdodecyl sulphate (SDS)). We took out the right amounts at the right times in aliquots (5, 10, 15, 20, 25, 30 min.) The research kept the sink at the same temperature and pressure. After collecting 5 ml of the samples, they were filtered using a 0.45 mm Millipore filter. To keep the volume of the solution constant, 5 ml of new dissolution fluid was added to the solution. Afterwards, a UV/visible spectrophotometer was used to examine the samples at a max wavelength of 248 nm.

Fourier transforms infrared spectroscopy

Bruker Alpha FTIR was used to collect the spectra. Apixaban or SDs were pulverised and completely mixed with potassium bromide, an infrared transparent matrix, at a 1:5 (Sample/KBr) ratio. It took 5 minutes and 5 tonnes of pressure in a hydraulic press to turn the particles into KBr discs.

Apixaban rapid-release tablet formulation

according to Table, were made with variable quantities of various formulation components. No. 9. Everything must pass through an 80-mesh screen. API, polymer, and mannitol are thoroughly combined, blended, greased with Magnesium stearate, and then squeezed in a proton micro press

10 station tablet punching machine.

INGREDIENTS(in mg)	FORMULATION BATCHES											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Apixaban	10	10	10	10	10	10	10	10	10	10	10	10
MCC PH 102 (Avicel 102)	190	190	190	190	190	190	190	190	190	190	190	190
Polyplasdone XL (Crosporidone XL-10)									4	8	12	16
Croscarmellose sodium (CCS)	4	8	12	16								
Sodium Starch Glycolate (SSG)					4	8	12	16				
Mannitol	87	83	79	75	87	83	79	75	87	83	79	75
Magnesium Stearate	2	2	2	2	2	2	2	2	2	2	2	2
Aspartamate	7	7	7	7	7	7	7	7	7	7	7	7
Average Weight	300	300	300	300	300	300	300	300	300	300	300	300

EVALUATION

- Combination of SD (SD5) and Excipient's pre-compression parameters
- Assume a horizontal position with a 45-degree angle of repos
- Put 5 grammes of powder into a cone-

Indo-American Journal of Pharma and Bio Sciences

Vol. 20, Issuse 4, Nov 2022

shaped funnel and secure it to a holder 6 centimetres from the ground. Set a graph paper down underneath it. The funnel was used to carefully move the sample through. There was a rise in the powder pile's height. Next, use a pencil to make a rough sketch of the pile on the graph paperin order to determine its diameter. The distance around the mound was calculated. Using this formula, we can get the angle of repose. For precision, this is done five times.

Indo-American Journal of Pharma and Bio Sciences

Vol. 20, Issuse 4, Nov 2022

$$\emptyset = \text{Tan}^{-1} h/r$$

Where, h = height of file

R= radius of the base of the pile Ø = angle of repose

The results were tabulated in table.

Bulk density and Tapped density:

Very carefully, a known weight (w) of powder was poured into the graduated cylinder, and the resulting volume (v0) was recorded. The graduated cylinder was then sealed with a cover, placed in the density determining device (Bulk density apparatus), and run for 500 taps, after which the volume (vf) was measured, and the process was repeated until the two subsequent readings were the same. The following equations were used to get the bulk density and tapped density.

$$\text{Bulk Density} = W/V_0$$

$$\text{Tapped Density} = W/V_f$$

Where, V_0= Initial volume,

V_f = final volume

The results were tabulated in table.

Assessment of Apixaban Tablet Formulation

The following official and unofficial metrics were used to assess all of the sustained-release tablet formulations.

The Weight Can Vary

Every batch had twenty pills weighed, at random. Twenty pills' average and standard deviation in weight were determined. If no more than two tablets in a given batch have weights that differ from the batch average by more than twice the percentage depicted in a none deviation from the mean weight chart, then the batch passes the weight variation test.

$$\% \text{ deviation} = \frac{\text{tablet weight-average weight}}{\text{Tablet weight}} \times 100$$

Observation:

The average weight and standard deviation of the tablets of each batch were given.

Weight variations Specification

Table.No.:10. Weight variations Specification

Average weight of tablets(X mg)	Percentage deviation
130 or less	±10
130 to 324	±7.5
More than 324	±5

Dimensions

For tablets to be widely accepted by consumers and for there to be consistent quality amongst tablets, the thickness must be carefully managed. Digital Vernier callipers were used to measure to the exacting standards. It is possible to employ tablet thickness as a primary control parameter because of its correlation to tablet hardness. Digital Vernier callipers were used to measure the thickness of six tablets taken at random from each batch. Hardness The product's form and design, as well as its compactness during transport, coating, and packing, are crucial. A hardness tester was used to get the results. Pfizer hardness testers were used to examine six pills from each batch. The tablet's breakage force is measured in kilogrammes per square centimetre, or Kg/cm2. It was observed that the average hardness of the tablets in each batch was between 6 and 16Kg/cm2.

CONCLUSIONS AND RESULTS

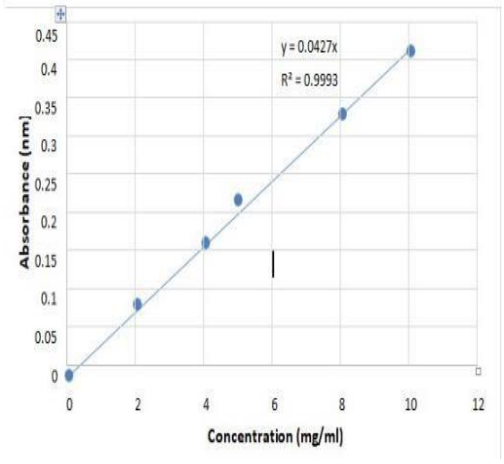
Curve of calibration for Apixaban

S. No.	Concentration (µg/ml)	Absorbance (nm)
1	0	0
2	2	0.093
3	4	0.174
4	5	0.215
5	8	0.341
6	10	0.424
Slope	**0.0427**	

Calibration curve of apixaban

Indo-American Journal of Pharma and Bio Sciences

Vol. 20, Issuse 4, Nov 2022



CONCLUSION

The aim of this research was to develop and assess Apixaban quick release tablets. The Direct compression approach utilised in tablet formulation proved to be the most effective in all cases. Organo-leptic bulk density, angle of repose, tapped density, compressibility index, hausner ratio, melting point range, pH, and solubility experiments were performed prior to formulation per USP requirements. It was found via physical testing that the drug excipients were compatible with one another, and that the combination had not changed significantly. In the experiments, scientists used polymers such Polyplasdone (Crospovidon-XL), Croscarmellose Sodium (CCS), and Sodium Starch Glycolate (SSG). All three polymers used underwent the same battery of physical tests as part of the exhaustive preformulation research. The results for all the different formulations were within the allowable margin of error. Dissolution experiments, as well as assessments of tablet weight, hardness, friability, thickness, and thickness, were conducted. The tests of release were performed in 7.4 pH Saline for 20 minutes. Testing of samples for all three polymer types. Formulation F12, which only contains Crospovidon-XL, was shown to have a 98.14% release within 8 minutes. The results of the assay showed that Formulation F12 had a success rate of 96.12%. The release profiles for the remaining formulations were inconsistent. After all the tests were done, it was decided that F12 was the best formulation.

REFERENCES

[1]. Remington, The Science and pharmacy practice of Pharmacy, 21st edition volume, I, II, 869-870.

[2]. Kewel K Jain, Drug delivery system, Third Edition,217-219.

[3]. Lachman, L., Liberman, H.A., and Kanig, J.L. The Theory and Practice of Industrial Pharmacy, Lea Febiger, Philadelphia. 293- 294,226-328.

[4] . Verma, R. K., and Garg, S., Current status of drug delivery technologies and future directions, Pharmaceutical Technology On- Line, 2001,1-14.

[5]. Bryan, J.W., Enhancement & Controlled Release as Synergistic Tools Bioavailability enhancement, Drug Delivery Technology, 2002, 2, 6.

[6]. Himanshu Gupta, Dinesh Bhandari and Aarti Sharma, Recent Trends in Oral Drug Delivery: A Review, Recent Patents on Drug Delivery & Formulation 2009, 3, 162-173

[7]. Jain N.K. Mucoadhesive drug delivery. In: Ahuja A., Ali J., Khar R.K., editors. Progress in controlled and novel drug delivery systems. New Delhi: CBS publishers and distributors; 2004.

[8]. Arunachalam A., Ashutoshkumar S., Karthikeyan M., Konam K., Prasad P.H., Sethuraman S. Solid Dispersions: A Review. Current Pharm Research 2010; 1, 82-90.

[9]. Huda N.H., Saffoon N., Sutradhar K.B., Uddin R. Enhancement of Oral Bioavailability and Solid Dispersion: A Review. Journal of Applied Pharm Sci.2011; 1, 13-20.

[10]. Baghel R.S., Singh S., Yadav L. A review on solid dispersion. Int J of Pharm & Life Sci.2011: 2, 1078-1095.

[11]. 5. Price JC, Polyethylene glycol, in: A. Wade, P.J. Weller (Eds.), Handbook of Pharmaceutical Excipients, American Pharmaceutical Association/The Pharmaceutical Press, Washington, DC/London, 1994; pp. 355-61.