IJPSR (2020), Volume 11, Issue 12 **(Review Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 25 June 2019; received in revised form, 10 October 2020; accepted, 24 November 2020; published 01 December 2020

A NOVEL APPROACHES FOR DRUG DEVELOPMENT AND PHARMACOLOGICAL STUDY OF HERBAL PLANT

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Keywords:

OECD, Pharmacokinetic, Ash value, Nanoparticles and diabetes

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ABSTRACT: From ancient times, herbal medicines are in use to cure the diseases due to their impending and less side effects. But complications in identification, processing, standardizing, extracting of herbal drugs, it seldom attracts scientists towards the development of novel delivery systems for herbal drugs. During drug development, the complete knowledge of novel scientific approaches like toxicity study, OECD guidelines, pharmacokinetic, drug and cosmetic act as well as different types of formulation are necessary to understand. Here, we have tried to compile all the drug preparation methods in brief. Nanoparticles are in the solid state and are amorphous or crystalline. They are capable to absorb and/or encapsulate a drug in large amount with increased pharmacodynamic and pharmacokinetic action. Thus protecting it against chemical and enzymatic degradation Also, given some information about types of diabetes and its pathophysiology. In advanced novel drug delivery system microspheres playing a very vital role having maximum loading capacity and are easily formulated with natural as well as synthetic polymers.

INTRODUCTION: In recent years, Scientific Society is lengthily involved in the research and development of novel approaches to delivering herbal drugs. The Natural product isolated from the plants are known as herbal drugs and are the core of the traditional medicinal system that is being pursued from ancient times. With the development of Science and technology in the field of formulation technology of drug products, a day's herbal dosage form has evolved from simple mixture, pills, tablets, and capsule to highly sophisticated technology-based drug delivery system.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.11(12).5974-86

This article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.11(12).5974-86

Here in this paper, we have reviewed the earlier work carried out as well as pharmacognostical characteristics of this plant with new pharmaceutical techniques be explained. The novel approach means latest guidelines, latest formulation preparation such as nanoformulation *etc*. are described in this chapter. Based on the earlier reports, we have found that *Pueraria tuberosa* is an important drug of Ayurveda.

Various types of pharmaceutical preparations, tablets, capsules some nano preparation are in clinical use, but their pre-clinical toxicity studies and pharmacokinetics have not been done as per recently implemented OECD guidelines.

Novel herbal drug delivery system is designed to passive the limitation of the currently available herbal drug formulation due to its extensive range of advantage to mankind can be summarized as follows:

The novel herbal drug delivery system can be used to accomplish site-specificity. Novel drug delivery system enhances the surface area of the drugs, therefore allows quicker absorption and rapid onset of action. The enhanced penetration of nano-particles through the Blood Brain Barrier.

Nanoparticles: Nanoparticles (including nano-spheres and nanocapsules of size 10-200 nm) is in the solid-state and are either amorphous or crystalline. They are capable of absorbing and/or encapsulate a drug, thus protecting it against chemical and enzymatic degradation.

In recent years, biodegradable polymeric nano-particles have attracted considerable attention as potential drug delivery devices in view of their applications in the controlled release of drugs, in targeting particular organ / or tissue, as carriers of DNA in gene therapy, and in their ability to deliver proteins peptides and genes through per oral route [1].

Classification of Nanomaterials:

A. Nanotubes: They are hallowing cylinders prepared of carbon atoms. They can also be filled and sealed, forming test tubes or potential drug delivery devices.

B. Nanowires: Glowing silica nanowire is wrapped around a single strand of human hair. It looks delicate. It is about five times smaller than virus applications for nanowires include the early sensing of breast and ovarian malignancies.

C. Nanocantilever: The honeycomb mesh behind this tiny carbon cantilever is the surface of the fly's eye.

Cantilevers are beams anchored at only one end. In the nano-world they function as sensors ideal for detecting the presence of extremely small molecules in a biological fluid.

D. Nanoshells: Nanoshells are hollow silica spheres covered with gold. Scientists can attach antibodies to their surfaces, enabling the shells to target certain shells such as cancer cells. Nanoshells one day also are filled with drug-containing polymers.

E. Quantum Dots: Quantum dots are minuscule semiconductor particles that can serve as signposts of a certain type of cells or molecules in the body. They can do this because they emit different wavelengths of radiations depending upon the type of cadmium used in their cores. Cadmium sulphide for ultraviolet to blue, cadmium selinide for most of the visible spectrum and cadmium telluride for far infra red and near infra red.

F. Nano Pores: Nanopores have cancer research and treatment applications. Engineered into particles, they are holes that are so tiny that DNA molecules can pass through them one strand at a time, allowing for highly precise and efficient DNA sequencing. By engineering nanopores into the surface of drug capsules that are only slightly larger than medicine's molecular structure, drug manufacturers can also use nanopores to control the rate of drug diffusion in the body.

G. Gold Nanoparticles: These nanoparticles seen in transmission electron micrograph images; they have a solid core. Research at north-western university is using gold particles to develop ultra-sensitive detection systems for DNA and protein markers associated with many forms of cancer, including breast, prostate cancer.

H. Bucky Balls: Buckyball is common for a molecule called buckminsterfullerene, which is made of 60 carbon atoms formed in the shape of a hollow ball discovered in 1985. Buckyballs and other fullerenes, because of their chemistry and their unusual hollow cage-like shape extremely stable and can withstand high temperatures.

I. Applications: Buckyballs may see wide-spread use in future products and applications, from drug delivery vehicles for cancer therapy to ultra-hard coating and military harmor.

Bucky Ball: Antibody combination delivers anti-tumor drugs.

- Buckyballs to fight allergy.
- Bucky balls as powerful antioxidants and also inhibitor of HIV.

Demerits:

- Buckyballs hurt cells.

- Buckyballs have a high potential to accumulate in living tissue.
- Difficulty of targeting drug delivery location.

Carbon Nanotubes: Carbon nanotubes can be modified to circulate well within the body. Such modifications can be accomplished with covalent or non-covalent bonding. Modifications can increase or decrease circulation time within the body. Carbon nanotubes no significant toxicity when they have modified so as to be soluble in aqueous body type fluids. They enter readily into the cells. Cancer cells in the tumor are larger than normal cells and also exhibit leakage. Large molecules that circulate slowly can leak into and accumulate in the cancer cell. Carbon nanotubes carrying active agents have been demonstrated in animal studies to do this. Researchers have also used carbon tubes to deliver the precursors of active drugs, which they call a prodrug. *E.g*: Cisplatin [27].

Toxicity: Ayurvedic medications have the prospective to be toxic [2]. Many materials used in them have not been thoroughly studied in either Western or Indian research. In the United States, Ayurvedic medications are regulated as dietary supplements. As such, they are not required to meet the safety and efficacy standards for predictable medicines. An NCCAM-funded study published in 2004 found that of 70 Ayurvedic remedies purchased over-the-counter (all manufactured in South Asia), 14 contained lead, mercury and/or arsenic at levels that could be harmful [3]. Also, in 2004, the Centres for Disease Control and Prevention reported that 12 cases of lead poisoning occurring over a recent 3 year period were linked to the use of Ayurvedic medications.

Toxicity Study Related to Any Drug for Human use why it is Important: Toxicology is an area of science that deals by means of toxin and poisons and their effect and treatment. Toxicology screening is very significant for the development of new drugs and for the extension of the therapeutic prospective of existing molecules. The US Food and Drug Administration (FDA) state that it is necessary to screen new molecules for pharma-cological activity and toxicity perspective in the animal. The toxic effect of chemical food substances, pharmaceuticals, *etc*., has attained enormous significance in the 21st century. Toxicity tests are mainly used to study specific adverse events or specific endpoints such as cancer, cardio-toxicity, and skin/eye irritation. Toxicity testing also helps analyze the No Observed Adverse Effect Level (NOAEL) dose and is obliging for a clinical study.

Introduction of OECD Guidelines: The OECD guidelines are a unique tool for assessing the potential effect of chemicals on human health and the environment. Accepted internationally as standard method for safety testing, the Guidelines are used by professionals in the industry, academia, and government involved in the testing and assessment of chemicals (industrial chemicals, pesticides, cosmetics, *etc*.). These Guidelines are regularly updated with the assistance of hundreds of national experts from OECD member countries.

OECD 425 Acute Toxicity Studies by Up and Down Method: OECD guidelines for the Testing of Chemicals are periodically reviewed in the light of scientific advancement or changing assessment practices. The perception of the up-and-down testing approach was first described by Dixon and Mood [4, 5]. In 1985, Bruce projected to use an up-and-down procedure (UDP) for the determination of the acute toxicity of chemicals.

There subsist several variations of the up and - Down experimental design for estimating an LD50 (OECD 425). This guideline is based on the procedure of Bruce as adopted by ASTM in 1987 and revised in 1990. A study comparing the results obtained with the UDP, the conventional LD_{50} test, and the Fixed Dose Procedure (FDP, Guideline 420) was published in 1995. Since the earliest papers of Dixon and Mood, papers have sustained to appear in the biometrical and applied literature, examining the best situation for the use of approach [6].

OECD 407 - Repeated dose Toxicity Study: OECD Guidelines for the Testing of Chemicals are periodically reviewed in the light of scientific improvement. Guideline 407 was adopted in 1981. In 1995 a revised version was adopted to obtain supplementary information from the animal used in the study, in particular on neurotoxicity and immunotoxicity [7].

(I) Principle of the Test: The test substance is orally administered daily in graduated doses to numerous groups of experimental animals, one dose level per group for a period of 28 days. During the period of administration, the animals are observed each day closely for signs of toxicity. Animals that die or are euthanized during the test are necropsies, and at the conclusion of the test, surviving animals are euthanized and necropsied. A 28-day study provides information on the effects of repeated oral revelation and can indicate the need for further longer-term studies. It can also give information on the selection of dose concentration for longer-term studies. The data derived from using the TG should allow for the characterizations of the test substance toxicity, for an indication of the dose-response affiliation and the determination of the No-Observed Adverse Effect Level (NOAEL) [8]. A median lethal dose for each rat, the observation was made for 24 h, and symptoms of toxicity and rate of mortality in each group were noted. At the end of the study period, expired animals were counted for the calculation of LD_{50}. The arithmetic method of Karber was used for the determination of LD_{50}.

$$LD_{50} = LD100 - (a \times b)\ n$$

n = total number of animals in a group. a = the difference between two successive doses of administered extract/substance. B = the average number of dead animals in two successive doses. LD 100 - Lethal dose causing the 100% death of all test animals.

Limit Test: The limit test is primarily used in situations where the experimenter has information indicating that the test material is likely to be nontoxic, *i.e.,* having toxicity below regulatory limit doses. Information about the toxicity of the test material can be gained from information about similar tested compounds or similar tested mixtures or products, taking into consideration the identity and percentage of components known to be of toxicological importance.

Principle of the Limit Test: The limit test is a chronological test that uses a maximum of 5 animals. A test dose of 2000, or exceptionally 5000 mg/Kg, may be used. The procedures for testing at 2000 and 5000 mg/kg are slightly different. The selection of a sequential test plan increases the statistical influence and also has been made to intentionally bias the procedure towards rejection of the limit test for compounds with LD_{50} near the limit dose, *i.e.,* to err on the side of safety. As with any limit test protocol, the possibility of correctly classifying a compound will decrease as the actual LD_{50} more nearly resembles the limit dose.

Drug & Cosmetic Act 1940: The Drug & Cosmetic Act, 1940 is an Act of the Parliament of India which legalizes the import, manufacture, and distribution of the drug in India. The primary goal of the act is to ensure that the drug and cosmetics sold in India are safe, effective, and conform to the state qualifying standard. The related Drugs and cosmetic rules 1945 contain a prerequisite for the classification of a drug under a given schedule, and there are guidelines for the storage, sale, display, and prescription of each schedule. This act was first known as the Drug Act and was passed in 1940. The original act was prepared in accordance with the suggestion of the Chopra Committee formed in 1930. The related Drugs Rules were passed in 1945. Since 1940, the Act has undergone several amendments and is now known as the Drug and Cosmetic Act, 1940 [9]. The term "drug" as defined in the act includes a wide variety of substance, diagnostic, and medical devices. The act defines "cosmetic" as any product that is designed to be applied to the human body for the purpose of beautifying or cleansing. The definition, however, excludes soaps. In 1964, the act was amended to include Ayurveda and Unani drugs.

The Drugs and Cosmetics (10th Amendment) Rules, 2017: This amendment is effective from March 27, 2017. However, the CDSCO has published the following interim guidelines to make sure the soft processing of applications for grant of manufacturing licenses and for the joint examination of manufacturing premises.

1. Application for the allowance of manufacturing licenses, complete in all respect as per the provisions of the Drug and Cosmetic Act, 1940 and Rules, 1945, should be submitted by the manufacturer to the particular State Licensing Authority.
2. The State Licensing Authority should fix a date at least seven days prior to the date of joint inspection of the manufacturing premise,

in coordination with the respective zonal/sub-zonal officer of CDSCO.

3. In case the drug inspector of CDSCO zonal/sub-zonal officer is not available on any particular date, a drug inspector from CDSCO (HQ) will be deputed for the joint inspection.
4. Suitable coordination between State Licensing Authorities, CDSCO HQ, and Zonal/Sub-zonal officers should be ensured for timely inspection and processing of applications.
5. In case of insufficiency in the application in respect of any inspection, the joint inspection team may verity such a document during the inspection and record detail of the same in the inspection report [22].

Schedule - Y: It contains necessities and guidelines for consent to import and/or manufacture of new drugs for sale or to undertake clinical trials. Schedule Y, the current regulator (CDSCO - Central Drugs Standard Control Organization) enforced the law in India, has been renowned under the Drugs and Cosmetic Act 1945. The regulations to be followed when conduct clinical trials in India are clearly renowned to a large extent in this document. Schedule Y for India is a law and not a mere guideline. The enforcement that came into existence in 1988 was a vital provision for providing support to the upscale of generic pharma present in those days. With the entry of large pharmaceutical companies along with the multiple multinationals in the field of clinical research, the requirements changed, and a revised version of Schedule Y in line with ICH-GCP (International Council of Harmonization and Good Clinical Practice) standard was put forth in 1995.
Since then, many revisions to schedule Y took place to provide a healthy environment for clinical research to be conducted in India [10].

The 2005 version of Schedule Y has the three most important sections and eleven appendices.

- Application for permission
- Clinical Trial
- Studies in Special populations

With the recent advancements in its operations, DCGI (Drugs Controller General of India) has taken multiple steps to steer the clinical research industry in the exact direction. Steps such as registration of contract research organizations (CRO's) with DCGI, auditing clinical trials during their conduct, create guidelines for ethics committees to control cleanly, and many such proposed ideas will surely help the Indian clinical research industry to boost itself. Implementation of these raises the bar for the industry to the role as per quality standards expected by the foreign regulators. Mandatory registration of clinical trials in the Clinical Trial Registry of India (CTRI) has already made the procedure transparent and evolved it to the next level. The evolution of regulatory systems will help India to tap its potential in unmarked areas like nutraceutical and drug development in herbal (alternative) systems of medicines [11]. DCGI still has numerous concerns towards creating a better law enforcer, a better Schedule Y, which will happen with further revisions of the Schedule Y document in the future. The pillars in conducting research, such as ethics committees and knowledgeable consent, are to be strengthened to maintain patient safety along with the collection of quality data. A vigilant and evolving robust regulatory system is the need of the hour for the current regulatory scenario to benefit. Till recent times, the fundamental responsibility of Good Clinical Practice compliance used to lay with the sponsor alone; however, with the current advancements in Schedule Y, GCP compliance is turning out to be a collective responsibility of all stakeholders such as the sponsor, investigator, regulatory authority and ethics committees.

Pharmacokinetics: Pharmacokinetics may be defined as the quantization of the time course of a drug and its metabolites in the body or body fluid and the improvement of an appropriate model to describe observation and to expect the outcome in other situations. The science of kinetics deals with the mathematical explanation of the rating process of a reaction. A typical example of naturally occur-ring method of pharmaceutical interest which confirm to first - order kinetic are radioactive decay of materials and the absorption, distribution, metabolism and excretion (ADME), of drug in the body. The pharmacokinetics rate constant is dependent relative to the concentration or amount of only one component of the system [23]. The kinetics pursues first order or pseudo-first pro-cesses not necessarily because they are so simple, but due to the fact that all other components of the

system or model except the drug concentration are constant. Thus most *in-vivo* drug possess, especially the (ADME), pursue pseudo-first-order process [12].

Pharmacokinetic Functional Equations: In mathematical terms, the rate law for a first-order process can be expressed in terms of a small infinitesimal alteration in concentration (dC) over an infinitesimally small time interval (dt) as;

Rate = dC/dt = - KC…….Eqn. 1

Where K is the first-order rate constant. This is the differential rate expression for a first-order process.

Upon integration, this yield as,

Ln C = Ln Co- Kt…….Eqn. 2

But Ln X = 2.303 Log X, hence;

Log C = Log Co – Kt / 2.302

Equation 2 is the integrated form of the first-order rate law, which is linear. The exponential form of the rate equation for a first-order process is expressed as;

C = Co e - Kt…….Eqn. 3

Taking the natural logarithms on both sides of Eqn 3 yields;

Ln C = Ln Co - Kt.

This is the same as Eqn 2. Multiplying both sides of Eqn 3 by V, the total volume of distribution;

VC= V Co e - kt

A= DOSE e – kt……Eqn 4

Rearrange this equation yield;

A/DOSE = e – kt

Which is the fraction of the dose remaining at time t? Where A, is the amount of the drug in the body at time t, V is the total volume of distribution, C is the plasma conc. at time t and Co is the initial plasma conc. At the time to.

Half - life (t1/2)

The time required for the plasma concentration (C), to drop to half the imaginative plasma concentration, (C/2), is called the half-life (t 1/2). For a first-order process, this parameter is constant. Theoretically, a first-order process never reaches completion since even the smallest concentration would only fall to half its value in one half-life. For most practical purposes, a first-order process may be deemed "complete" if it is 95% or more complete. It has been established that to attain this level of completion, at least five half-lives must elapse [20]. In the urinary analysis, total urine collection is effected or deemed complete after at least five half-lives of the collection period. The connection between half-life (t1/2) and rate constant, k, is also a very useful working pharmacokinetic equation and is defining as;

T1/2 = 0.693/ k and k = 0.693/t1/2.

The volume of distribution (Vd) - The volume of plasma in which a drug distributes in the body at equilibrium is called the total volume of distribution, Vd. However, the apparent volume in plasma of drug distribution in the body at equilibrium referred to as the apparent volume of distribution Vd. Thus the concentration in plasma, C, achieved after distribution equilibrium is complete is a function of the amount of drug in the body, A (or dose) and the extent of distribution of the drug into the tissue, V. Mathematically, this is expressed as;

V = A / C and at zero time,

Vd = Dose / Co.

Where Co is the initial plasma concentration at zero time to the total volume of distribution V, may also be defined as the proportionality const between the plasma concentration C and the quantity of drug in the body, A.

Clearance CL: This is the proportionality factor or renovation factor which relates the plasma concentration, C, to the rate of drug elimination, dA/dt.

Thus Rate of elimination,

dA/dt = CLT.C.

Mathematically, clearance total is articulated as;

CLT= k. V

Owing to the additive concept of clearance, the total clearance, CLT, can be expressed as the sum of metabolic clearance, CLM and renal clearance, CLR. Thus,

$$CLT = CLM+CLR$$

Dosage Form: All pharmaceutical products are formulated to definite dosage forms for drugs to efficiently deliver to the patient. The pharmaceutical dosage forms include oral tablets, capsules, solution, suspension, topical ointment, gels, and solution and parenteral injection for intravenous (IV): Intramuscular (IM), or subcutaneous (SC) administration [13]. In pharmaceutics, the pharmaceutical formulation is the process in which different chemical substances, including the active constituents, are collective to manufacture a final medicinal product. The word formulation is often used in a technique that includes dosage form.

Types of Dosage form: The main dosage form divided into three groups.

1. Solid
2. Liquid (Parentaral)
3. Semisolid

Tablets: A tablet is a pharmaceutical dosage form. Tablets may be defined as the solid unit dosage form of medicament or with or without suitable excipients and prepared either by molding or by compression. It comprises a mixture of active substances and excipients, usually in powder form, condensed from a powder into a solid dose. The excipients can include diluents, binders, glidants (flow aids) and lubricants to ensure efficient tableting; disintegrates to promote tablet break-up in the digestive tract; sweeteners or flavors to increase taste and pigments to make the tablets visually attractive or aid in visual identification of an unknown tablet. A polymer coating is often applied to make the tablet smoother and easier to swallow, to control the release rate of the active ingredient, to make it more resistant to the environment (extending its shelf life), or to enhance the tablet's appearance [14]. Tablets are prepared mainly by compression of granules of powder blends, with a limited number prepared by molding. Chiefly tablets are used in the oral administration of drugs. Many of these are ready with colorants and coatings of various types'. Other tablets, such as sublingual, buccal, or vaginal tablets, are prepared to have featured most related to their particular route of administration.

General Properties of Tablets: A tablet must be strong and hard to resist mechanical shock during development, packing, shipping, dispensing, and use. The drug content of the tablet must be bioavailable; that is, the tablet must be able to release its content in an expected and reproducible manner. The tablet must be chemically and physically stable to maintain its chemical and physical attributes during manufacture, storage, and use. Tablets must be uniform in weight and in drug content.

General Appearance: The general appearance of the tablet, its visual identity, and overall is important for consumer acceptance, for control of lotto lot consistency and general tablet to tablet uniformity and for monitoring trouble-free manufacturing.

Size and Shape: The size and shape of the tablet can be dimensionally described, monitored, and controlled. A compressed tablet's shape and dimensions are determined by the tooling during the compression process.

The thickness of a tablet is the only dimensional variable process. The crown thickness of individual tablets may be measured with a micrometer, which permits accurate measurement and provides information on the variation between tablets.

Unique Identification Marking: This marketing utilize some form of embossing, engraving, or printing. A look into the product identification section of the correct observation Desk Reference (PDR) [14] provides a quick reference to the multitude of marking variations that can be produced. The types of informational marketing placed on a tablet usually include the company name or symbol.

Types of Tablets:

1. **Compressed Tablets:** Compressed tablets represent a significant quantity of tablets that clinically provide universal administration of therapeutic agents either in an uncoated state (*i.e.,* in their simplest form) or in a coated state. Compressed tablets are formed by

compression of powdered, crystalline, or granular materials into the requisite geometry by the application of high pressure, utilizing steel punches and die.

2. **Sugar-coated Tablets:** These are compressed tablets that have been coated with a concentrated sugar solution to recover patient's compliance, increase aesthetic appeal, mask object ableterstesor odors, increase stability and /or modify the liberate of therapeutic agents.
3. **Film-Coated Tablets:** coated tablets are expected tablets coated with a thin layer of polymer (*e.g.*, hydroxypropyl methylcellulose, hydroxypropyl cellulose) or a mixture of polymer (*e.g.*, Eudragit E 100) able of forming a skin-like film. The film is generally colored and also impacts the same general character as sugar coating with the extra advantage of being more durable, less bulky, and less consuming to concern.
4. **Effervescent Tablets:** Those tablets are uncoated tablets that usually include organic acid (such as tartaric or citric acid) and sodium bicarbonate in adding together to the medicinal substance or API. They react quickly in the occurrence of water by releasing carbon dioxide, which acts as a disintegrator to produce either a drug suspension or an aqueous solution.
5. **Enteric Coated Tablets:** Those are compressed tablets that have belated release properties.

   They are coated with the polymeric material (such as cellulose, acetate phthalate/cellulose acetate butyrate; hydroxyl-pro-phenylmethyl cellulose succinate, and metha-rylic acid copolymers) that resist solution in gastric but disintegrate and permit drug dissolution and absorption in the intestine
6. **Chewable Tablets:** Chewable tablets are big sized tablets which are not easy to swallow and thus, are chewed within the buccal cavity prior to swallowing. They are mainly useful for the administration of large tablets to children and adults who have difficulty swallowing conventional tablets or antacid formulation in which the size of the tablets is normally huge, and the neutralization effectiveness of the tablet is related to particle size within the stomach.

Compressed tablets | **Sugar-coated tablets** | **Film-coated tablets**

Effervescent tablets | **Enter coated tablets** | **Chewable tablets**

FIG. 1: DIFFERENT TYPES OF TABLETS [21]

Tablets Excipients: In the tablet formulation, many materials are usually combined at various quantities to produce a tablet that is of a better standard. These materials serve a different and specialized function in the tablets.

Binders: *E.g*, include acacia gum, tragacanth, corn starch, methylcellulose, gelatin, ghatti gum, carboxymethyl cellulose, methylcellulose, polyvinyl-pyrrolidone and sugars like sucrose, glucose, dextrose, molasses.

Bulking Agents / Diluents / Fillers: *E.g*, anhydrous lactose, spray dry lactose, microcrystalline cellulose, corn starch, dicalcium phosphate, calcium sulfate, lactose, cellulose, mannitol, NaCl *etc*.

Lubricants: *E.g,* metallic stearate (0.1-0.2% w/w) *e.g,* magnesium stearate, calcium stearate, stearic acid (0.25-1%), hydrogenated vegetable oil, corn starch, boric acid, Nacl, sodium lauryl sulphate *etc*.

Glidants: *E.g,* Colloidal silicon dioxide, Cab -o-sil, Talc *etc*.

Colouring Agents: *E.g,* FD7 & C Blue No. 1, FD & C Blue No. 2, FD &C Green No. 3, D & C Green No. 5, D & C Red No. 6, D & C Red No. 21. D & C Red No. 22 *etc*.

Flavoring Agents / Flavorants: *E.g,* Aspartame (phizer).

Adsorbent: *E.g.,* silicon dioxide, magnesium oxide, starch, magnesium silicate *etc*.

Method of Tablets Manufactured: two standard methods have been reported for tablet preparation [14].

- Wet granulation
- Direct compression

Quality Control Test for Tablets: In tablet formulation development for the duration of development of tablet dosage forms, a number of quality control tests are performed to make that tablet produced to meet the requirement as specified in the official compendium and conformist requirement established by the industries. This test can be grouped into two broad categories -

- Pharmacopoeial or Official test
- Non-Pharmacopoeial or Non-official Test

Pharmacopoeial or Official Test: They are called official test because the test method is mentioned in official compendia such as the British Pharmacopeia, American Pharmacopoeias, *etc*.

TABLE 1: PHARMACOPOEIAL OR OFFICIAL TEST

USP Standards	Max % Difference Allowed	BP/IP Standards
130 mg or less	10%	84 mg or less
130 mg-324 mg	7.5%	84 mg-250 mg
More than 325 mg	5%	More than 250 mg

A-Weight Variation Testing: The test for uniformity of weight is conduct by weighing individually 20 tablets at random selected from a tablet batch and determining their individual weight. The individual weights are comparing with the average weight. The sample complies with USP standard if no more than 2 tablets are peripheral, the percent-tage limits, and if no tablet differs by more than 2 times the percentage limit.

B-Uniformity of Content: The Content uniformity test was developed to endorse content consistency of active drug substances within a narrow around the label claim under dosage. This test is important for tablets having a drug content of less than 2 mg or when the active ingredient comprises less than 2% of the total tablet weight. By the USP method, 30 tablets are erratically selected, 10 of these tablets are assayed according to the method explained in the individual monograph.

C- Disintegration Testing: For tablets, the first important step for drug dissolution is the breakdown of the tablets into granules or primary powder particles, a process known as disintergration. All USP tablets must pass a test for disintegration, which is conduct in vitro using disintegration test equipment.

The Equipment Cconsists of Basket: Rack assembly containing six open transparent tubes of USP- individual dimensions, held vertically upon a 10 mesh stainless steel wire screen. During the testing, a tablets is sited in each of the six tubes of the basket and through the use of a mechanical device, the basket is raised and lowered in a bath of fluid at 29 to 32 cycles per minute, the wire screen always below the level of the fluid, For most normal released tablets, under the permit able time.

D-Dissolution Testing: This test computes the amount of time mandatory for a given percentage of the drug substance in a tablet to go into solution under an accurate set of conditions. It is intended to make available a step toward the evaluation of the physiological availability of the drug substances. The dissolution medium for each drug is presented in the individual drug monograph. For basic drugs, acidic media are used while alkaline media are used in acidic drugs (*e.g.,* alkaline buffers). Drug with non-ionizing molecules, water is a good solvent. The dissolution rate test is conducted at 37 ± 1 ºC. The sample is removed from the dissolution chamber at periodic time intervals and assess for drug content using a UV spectrophotometer [24].

Microspheres: Microspheres are characteristically free-flowing powders consisting of proteins or synthetic polymers which are biodegradable in

nature and ideally having a particle size less than 200 μm. Materials used for preparing Microspheres are polymers. They are classified into two types:

1. Synthetic Polymers
2. Natural polymers

1. Synthetic Polymers are divided into Two Types:

1. Non-biodegradable polymers
2. Polymethyl methacrylate (PMMA)
3. Glycidyl methacrylate

Epoxy Polymers:

- ✓ Biodegradable polymers
- ✓ Lactides, Glycolides & their copolymers
- ✓ Poly alkyl cyanoacrylates
- ✓ Poly anhydrides

Synthetic Polymers: Poly alkyl cyanoacrylates is a potential drug carrier for parenteral as well as other ophthalmic, oral preparations. Polylactic acid is a suitable carrier for sustained release of narcotic antagonists, anti-cancer agents such as cisplatin, cyclo phosphamide and doxorubicin. Sustained-release preparations for the anti-malarial drug as well as for many other drugs have been formulated by using of co-polymer of polylactic acid and polyglycolic acid. Poly anhydride microspheres (40 μm) have been investigated to extend the precorneal residence time for ocular delivery. Poly adipic anhydride is used to encapsulate timolol maleate for ocular delivery. Poly acrolein microspheres are a functional type of microspheres. They do not require any activation step since the surfacial free CHO groups over the poly acrolein can react with the NH_2 group of protein to form Schiff's base. In the case of non-biodegradable drug carriers, when administered parent rally, the carrier remaining in the body after the drug is completely released poses the possibility of carrier toxicity over a long period of time. Biodegradable carriers which degrade in the body to non-toxic degradation products do not pose the problem of carrier toxicity and are more suited for parenteral applications

2. Natural Polymers Obtained from Different Sources Like Proteins, Carbohydrates and Chemically Modified Carbohydrates:

Proteins: Albumin, Gelatin, and Collagen

Carbohydrates: Agarose, Carrageenan, Chitosan, Starch

Chemically Modified Carbohydrates: Poly-dextran, Poly starch.

Natural Polymers: Albumin is a widely distributed natural protein. It is considered as a potential carrier of drug or proteins (for either their site-specific localization or their local application into discrete anatomical sites). It is widely used for targeted drug delivery to the tumor cells.

Gelatin microspheres can be used as an efficient carrier system capable of delivering the drug or biological response modifiers such as interferon to phagocytes. Starch belongs to carbohydrate class. It consists of the principle glucopyranose unit, which on hydrolysis yields D-glucose. It is a polysaccharide consist of a large number of free OH groups. By means of these free OH groups, a large number of active ingredients can be incorporated within as well as active on the surface of microspheres. Chitosan is a deacylated product of chitin. The effect of chitosan has been considered because of its charge. It is insoluble at neutral and alkaline pH values but forms salts with inorganic and organic salts. Upon dissolution, the amino groups of chitosan get protonated, and the resultant polymer becomes positively charged [27].

Diabetes: Diabetes is a type of metabolic syndrome that occurs either when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin that it produces. Insulin is a hormone that regulates blood sugar.

The increased production and ineffective scavenging of reactive oxygen species may play in a critical role in diabetes mellitus. The disturbance of the antioxidant defense system in diabetes is mainly because of alteration in anti-oxidant enzymes, impaired glutathione metabolism and decrease ascorbic acid levels. It is becoming the third "killer" of the health of mankind along with cancer, cardiovascular, and cerebrovascular diseases. On the basis of etiology and pathogenesis, diabetes is classified into two types- Type I and Type II. However, in both types, environmental factors and genetic susceptibility play an important role in the disease expression and the time of onset.

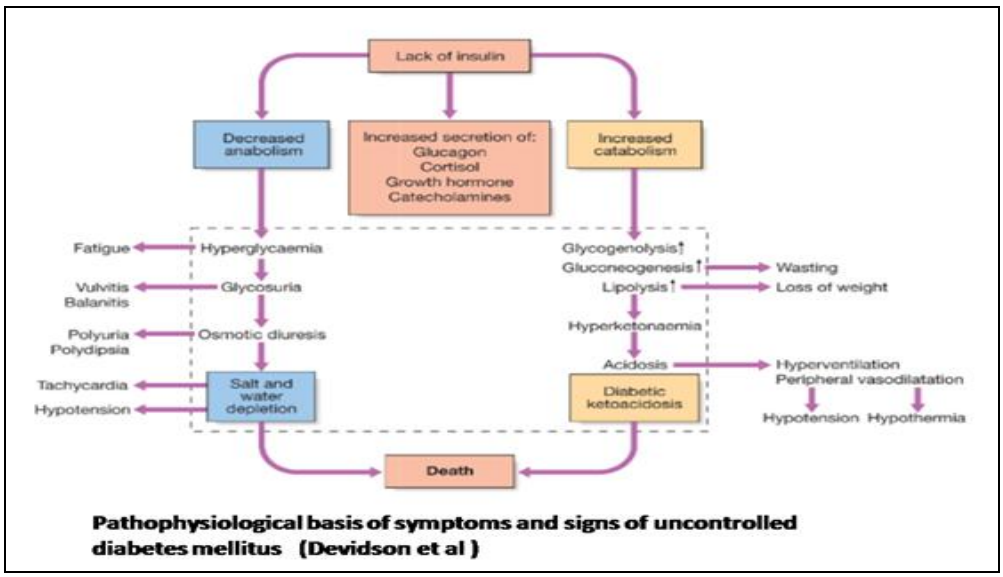

FIG. 2: PATHOPHYSIOLOGY OF DIABETES MELLITUS

Type I Diabetes Mellitus: It is an autoimmune disorder (T- cell-mediated) and involves the destruction of insulin-secreting ß-cells of the pancreas, thereby leading to profound insulin deficiency. Hence, it was earlier termed as "insulin-dependent diabetes mellitus". The classical symptoms develop only after the destruction of 70-90% of the ß cells. When progressive ß cell destruction crosses threshold level such that glucose cannot be maintained within the normal range, hyperglycemia ensues. It further, leads to glycosuria and dehydration. Extensive lipolysis and proteolysis cause weight loss, increased gluconeogenesis, and ketogenesis. When excess ketone body production interferes with the metabolism, ketoacidosis occurs. Symptoms include thirst, polyuria, fatigue, infections & weight loss.

Type II Diabetes Mellitus: It is more complex than type I diabetes. In this case, insulin resistance develops in liver and muscle. It is followed by an increase in insulin secretion. But, gradually, ß cell function gets impaired and the increased demand of insulin cannot be met, progressively leading to insulin deficiency. Since there is relative insulin deficiency, unrestrained lipolysis and proteolysis do not occur. There is a slow onset of hyperglycemia and the renal threshold for glucose rises. Thus, patients remain asymptomatic for a long time and present with complaints of fatigue, or without polyuria and polydipsia. If the patient presents at the stage when ß cell failure has reached, weight loss can be a symptom, but ketoacidosis is uncommon in this type

Herbal Materials: Herbal materials are either whole plants or parts of medicinal plants in the crude state. They include herbs, fresh juices, gums, fixed oils, essential oils, resins and dry powders of herbs, in some countries, these materials may be processed by various local procedures, such as steaming, roasting, or stir baking with honey, alcoholic beverages or other materials.

Herbal Preparation: Herbal preparations are the basis for finished herbal products and include comminute or powdered herbal materials, or extracts, tinctures and fatty oils expressed juices and processed exudates of herbal materials. They are produced with the aid of extractions, distillation, expression, fractionation, purification, concentration, fermentation or other physical or biological processes. They also include pre-parations made by steeping or heating herbal materials in alcoholic beverages and/or honey, or in other materials.

Complementary and Alternative Medicine (CAM): According to FDA guidelines, a group of diverse medical and health care systems, practices, and products that are not presently considered to be part of conventional medicine. It interprets "complementary" medicine as being used together with conventional medicine, whereas alternative" medicine is used in place of conventional medicine. National Center for Complementary and Alternative Medicine (NCCAM), USA classifies treatments based on the following or as a whole

Herbal Drug Standardization: Herbal medicines have been believed by many people to be natural and that medications of natural origin are not toxic or dangerous. There have been reports of acute and chronic intoxication resulting from the use of herbal remedies. Several researchers also reported that most herbal remedies exhibit organ-specific toxicity. Lack of standardization is a major concern regarding the use of medicinal herbal medicines [15]. Little is known about chronic toxicities that might be associated with their prolonged use. There has been minimal research to assess possible systemic toxicity that might be associated with high doses or due to chronic administration of products [16]. Since everything that enters the mouth is metabolized through the liver, the liver is a prime target for the toxic effects of some herbs. People with normal functioning livers and no history of prior liver disease have suffered adverse consequences to the liver as a result of taking certain herbs. The range of liver injury includes minor trans-aminase elevations, acute and chronic hepatitis, steatosis, cholestasis, zonal or diffuse hepatic necrosis, hepatic fibrosis and cirrhosis, veno-occlusive disease and acute liver failure requiring trans-plantation [17]. In addition to the potential for hepatotoxicity, drug-drug interactions between herbal medicines and conventional agents may affect the efficacy and safety of concurrent medical therapy.

Critical Factors Affecting the Quality Control of Herbal Drugs: Quality control of herbal drugs has traditionally been based on the appearance, and today microscopic evaluation is indispensable in the initial identification of herbs, as well as, in identifying small fragments of crude or powdered herbs and detection of foreign matter and adulterants [25].

(i) Moisture Content: Moisture content estimation is important; not only to know excess water but also in conjugation with appropriate temperature moisture will lead to the activation of the enzyme and gives suitable conditions to the propagation of living organisms. Various techniques for moisture determination are loss on drying, separation, and measurement, chemical method, electrometric method, and spectroscopic method [18].

(ii) Foreign Matter: Herbal drugs should be made from the stated part of the plant and be devoid of other parts of the same plant or other plants. They should be entirely free from mold or insects, including excreta and visible contaminants such as sand and stones, poisonous and harmful foreign matter, and chemical residues.

(iii) Ash Content: To determine ash content, the plant material is burnt, and the residual ash is measured as total and acid-insoluble ash. Total ash is the measure of the total amount of material left after burning and includes ash derived from the part of the plant itself and acid-insoluble ash. The latter is the residue obtained after boiling the total ash with dilute hydrochloric acid and burning the remaining insoluble matter.

(iv) Heavy Metals: Contamination by toxic metals can either be accidental or intentional. Conta-mination by heavy metals such as mercury, lead, copper, cadmium, and arsenic in herbal remedies can be attributed to many causes, including environmental pollution and can pose clinically relevant dangers for the health of the user and should, therefore, be limited [19]. The potential intake of the toxic metal can be estimated on the basis of the level of its presence in the product and the recommended or estimated dosage of the product [20].

CONCLUSION: Despite the benefits apart from the strict diet plan, standardization of herbal drug and their pharmacokinetic studies are required for the management of diabetes. By this mechanistic phenomenon, we will be able to develop a new and effective therapeutic approach to delay the progression of diseases. However, the feasibility and safety of these therapeutic approaches for formulation development and the clinical applicability of Indian herbal medicine in Diabetes need to be further investigated with experimental support.

ACKNOWLEDGEMENT: We have highly thankful Mr. Nikhil Pandey, Priyanka Mishra Department of Medicinal Chemistry, Smriti Singh Department of Kaumarya vrit, and Mr. Ravi department of Rachana Sharir IMS BHU.

CONFLICTS OF INTEREST: No potential conflicts of interest relevant to this article were reported.

Funding: Not applicable.

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How to cite this article:
Pandey H, Srivastava S and Tripathi YB: A novel approaches for drug development and pharmacological study of herbal plant. Int J Pharm Sci & Res 2020; 11(12): 5974-86. doi: 10.13040/IJPSR.0975-8232.11(12).5974-86.