3. LITERATURE REVIEW

Literature survey was carried out related to biopharmaceutical classification system, solubility, permeability, dissolution, method development, pharmacokinetics and nanoparticle formulation of herbal extracts and phytoconstituents. In this section the most relevant literature related to above mentioned topics was summarized.

3.1. Biopharmaceutical classification system

Blume et al., (2000)\textsuperscript{44} reviewed on scope of fitting herbal medicinal products in biopharmaceutical classification system. The authors gave a brief and thorough snapshot of all the difficulties in fitting herbal medicinal products into the concept of biopharmaceutical classification system and even highlighted the importance of fitting herbal medicinal products into biopharmaceutical classification system. They even emphasized that immediate release herbal medicinal products (85% release in 20 min) and herbal medicinal products with high soluble active ingredients can be waived from fitting into BCS. Hence, this review on the concept of herbal medicinal products is a defined valuable knowledge for formulators.

CDER (2000)\textsuperscript{7} U.S. Department of health and human services food and drug administration center for drug evaluation and research described guidance for industry provision for waiver of in vivo bioavailability and bioequivalence studies for immediate release solid oral dosage forms based on BCS. This guidance provides recommendations for sponsors of investigational new drug applications (IND’s), new drug applications (NDA’s), abbreviated new drug applications (ANDA’s), and supplements to these applications who wish to request a waiver of in vivo bioavailability (BA) and/or bioequivalence (BE) studies for immediate release (IR) solid oral dosage forms. These waivers are intended to apply to subsequent in vivo BA or BE studies of formulations after the initial establishment of the in vivo BA of IR dosage forms during the IND period, and in vivo BE studies of IR dosage forms in ANDA’s.

EMEA (2003)\textsuperscript{8} (The European Agency for the evaluation of medicinal products, evaluation of medicines for human use) characterized herbal extracts into standardized quantified extracts and mentioned special aspects related to solubility,
permeability, *in vitro* dissolution of herbal medicinal products as a pre-requisite for biopharmaceutical classification system.

Lindenberg *et al.*, (2004)\(^{45}\) reviewed the classification of orally administered drugs on the world health organization model list of essential medicines according to the biopharmaceutical classification system. They highlighted that 130 orally administered drugs on the WHO list, 61 could be classified with certainty, twenty-one (84\%) of these belong to class I (highly soluble, highly permeable), 10 (17 \%) to class II (poorly soluble, highly permeable), 24 (39 \%) to class III (highly soluble, poorly permeable) and 6 (10 \%) to class IV (poorly soluble, poorly permeable) and 28 drugs could be provisionally assigned, for 41 drugs are insufficient or conflicting data precluded assignment to a specific biopharmaceutical classification system class. They identified a total of 32 class I drugs (either certain or provisional classification) which were further considered for biowaiver status (drug product approval based on dissolution tests rather than bioequivalence studies in humans).

Shawahna *et al.*, (2011)\(^{46}\) demonstrated evaluation of the use of partition coefficients and molecular surface properties as predictors of drug absorption a provisional biopharmaceutical classification of the list of national essential medicines of Pakistan. They explained that partition coefficients (log \(D\) and log \(P\)) and molecular surface area (PSA) were potential predictors of intestinal permeability of drugs. The authors evaluated and compared these intestinal permeability indicators and concluded that Metoprolol as a permeability internal standard was more conservative than labetalol.

Wagh *et al.*, (2010)\(^{47}\) reviewed that biopharmaceutical classification system approach is meant to reduce unnecessary *in vivo* bioequivalence studies however, is restricted to non-critical drug substances in terms of solubility, permeability, and therapeutic range, and to non-critical pharmaceutical forms. The authors concluded that the *in vivo* performance of the drug depends upon its solubility and permeability, biopharmaceutical classification system is the guiding tool for the prediction of *in vivo* performance of the drug substance and development of drug delivery system to suit that performance.
Yasir et al., (2010)\textsuperscript{48} reviewed the principle, goal and guidance of biopharmaceutical classification system, characteristics of various biopharmaceutical classification system class drugs, various type of dissolution media for various biopharmaceutical classification system class drugs, their importance and methodology of dissolution, and various applications of biopharmaceutical classification system.

Dash and Kesari., (2011)\textsuperscript{49} described about biopharmaceutical classification system importance, its use in design and development of dosage forms. The authors explained the pivotal role of biopharmaceutical classification system in new drug discovery and lead optimization can be useful in gaining knowledge about solubility, permeability, bioavailability of drugs in human body, in clinical pharmacology (drug-drug, drug-food interaction) and also by regulation agencies of several countries as the scientific approach, for testing of waiver on bioavailability.

Reddy and Karunakar, (2011)\textsuperscript{50} reviewed that biopharmaceutical classification system is the step that reduces timelines in the new drug development process, both directly and indirectly and further reduces the unnecessary drug exposure in healthy volunteers, and increases impact for the replacement of certain bioequivalence (BE) studies with in vitro dissolution tests. They highlighted that biopharmaceutical classification system is useful for continuous efforts in mathematical analysis for the elucidation of the kinetics and dynamics of the drug process in the gastrointestinal tract (GIT) for NDA (New Drug Application) and ANDA (Abbreviated New Drug Application) filings and biowaivers.

Chen et al., (2011)\textsuperscript{51} reported that both biopharmaceutical classification system based permeability and biopharmaceutical drug disposition classification system, based metabolism can be used as a surrogate for extent of drug absorption and support for a waiver of in vivo bioequivalence studies. They discussed that specifically, if a drug is classified as high permeability under biopharmaceutical classification system or has high metabolism (≥ 90 %) under and biopharmaceutical drug disposition classification system, the extent of drug absorption is ≥ 90 %. They also explained that high metabolism in and biopharmaceutical drug disposition classification system may be supported by mass balance studies in humans, which includes measures of metabolites from CYP 450 and/or phase enzymes in the intestinal mucosa and/or
liver. European medicines agency, committee for medicinal products for human use 2007 provided guidelines on concept paper on biopharmaceutical classification system based biowaiver.

Kawabata et al., (2011)\(^5\) revealed the poor oral bioavailability arising from poor aqueous solubility should make drug research and development more difficult. The article described the basic approaches for poorly water-soluble drugs, such as crystal modification, micronisation, amorphization, self-emulsification, cyclodextrin complexation, and pH modification. This study revealed that classification of drug candidates based on their biopharmaceutical properties can provide an indication of the difficulty of drug development and useful for better understanding of the physicochemical and biopharmaceutical properties of drug substances and the limitations of each delivery option should lead to efficient formulation development for poorly water soluble drugs.

WHO (2011)\(^5\) General notes on Biopharmaceutics Classification System (BCS) - based biowaiver applications reported the scientific principles outlined in the guidelines listed above, the WHO Prequalification of Medicines Programme (PQP) has reviewed the available data related to the solubility, absorption, and dissolution characteristics of the medicinal products invited to the PQP evaluation, and has identified some active pharmaceutical ingredients to be eligible for biopharmaceutical classification system based biowaiver applications.

Darwhekar et al., (2012)\(^5\) demonstrated and classified Candesartan, an angiotensin II receptor blocker, as biopharmaceutical classification system class IV due to its inherent low bioavailability due to low solubility and low permeability. The results suggested that the prodrug used shows improved oral bioavailability which still remains to only 15 %. They characterized candesartan through biopharmaceutical classification system to find out the possible reasons for its poor bioavailability.

Waldmann et al., (2012)\(^5\) classified some markers of common herbs used in western medicine according to the biopharmaceutical classification system The results of this study demonstrated that a provisional biopharmaceutical classification system for classification of herbs is possible but some special considerations need to be included.
into the classification strategy and biopharmaceutical classification system can be used to choose appropriate quality control tests for products containing these markers. A provisional biopharmaceutical classification system for classification of twelve common herbs and their 35 marker compounds was provided in this article.

3.2. Permeability

Cook et al., (2003)\textsuperscript{56} investigated the intestinal permeability of chlorpyrifos (CPF), an organothiophosphate pesticide using the single pass intestinal perfusion (SPIP) technique in male, sprague dawley rats. SPIP was performed in each isolated region. Using established relationships, the human fraction dose absorbed for CPF was estimated to be 99%. The permeability values obtained from this study may be useful in models of exposure assessment.

Sharma et al., (2005)\textsuperscript{57} reviewed wide range of pharmacological activities of curcumin can be attributed to its potent antioxidant capacity at neutral and acid pH, its inhibition of cell signaling pathways at multiple levels, its diverse effects on cellular enzymes and its effects on angiogenesis and cell adhesion. In particular, curcumin ability to affect gene transcription and induce apoptosis in preclinical models advocates its potential utility in cancer chemoprevention and chemotherapy. They discussed that although curcumin low systemic bioavailability following oral dosing seems to limit the tissues that it can reach at efficacious concentrations to exert beneficial effects, the attainment of such levels in the gastrointestinal tract, particularly the colon and rectum, has been demonstrated in animals and humans.

Kale et al., (2007)\textsuperscript{58} described about reliable and predictive \textit{in vitro} methods to quantify drug transport across the intestinal epithelium are required at an early stage in the drug development process for oral solid dosage forms. In this work, an attempt has been made to develop an \textit{in vitro} continuous dissolution–absorption system to study the effect of slow drug release formulation variables on drug absorption. The dissolution studies were conducted on free drug and on two slow-release metformin hydrochloride (marketed) formulations. The studies yielded a dissolution–absorption relationship that can be used to predict dissolution or permeation-rate-limited absorption for two marketed formulations.
Patil et al., (2010) developed a simple, sensitive, specific, and reverse-phase high performance liquid chromatographic method for simultaneous analysis of caffeine, paracetamol and sulfasalazine, markers of high, medium and low intestinal permeability to determine their apparent permeability coefficient using rat everted gut sac technique. The obtained apparent permeability coefficient values can be correlated with human fraction absorption. The developed method for permeability markers can be used for high throughput cassette validation of intestinal permeability assessment.

Wahlang et al., (2011) demonstrated that curcumin a poly-phenolic compound possesses diverse pharmacologic activities; however, its development as a drug has been severely impeded by extremely poor oral bioavailability. Poor aqueous solubility and extensive metabolism have been implicated for this but the role of membrane permeability has not been investigated. These studies revealed that based on poor aqueous solubility and intestinal permeability, curcumin can be classified as a biopharmaceutical classification system Class IV molecule. This information can facilitate designing of drug delivery systems for enhancement of oral bioavailability of curcumin.

Milani et al., (2011) revealed that single pass intestinal perfusion technique (SPIP) is the most used classic technique employed in the study of intestinal absorption of compounds in which a non-absorbable marker such as phenol red is used to correct the water flux. A simple and rapid reversed-phase high performance liquid chromatographic method with UV detection at 227 nm was developed for simultaneous quantitation of Propranolol and Metoprolol along with phenol red for in-situ permeability studies. Using the SPIP technique and the suggested HPLC method for sample analysis, the mean values of 0.49 e-4 (±0.19) cm/sec and 0.32 e-4 (± 0.09) cm/sec were obtained for propranolol and metoprolol intestinal permeability coefficients respectively.

Wahajuddin et al., (2012) developed a simple, sensitive and specific RP-HPLC method for simultaneous determination of nine model compounds in permeability samples by using single pass intestinal perfusion study in rats. Stability studies were carried out at different storage conditions and all the analytes were found to be stable.
The method was successfully applied for analysing the permeability samples obtained from *in situ* single pass perfusion studies. The developed RP-HPLC method can be used for high throughput cassette validation of rat *in-situ* perfusion model for intestinal permeability assessment.

3.3. Dissolution

Muntaz *et al.*, (1995)\(^6^3\) reported a new and simple dissolution apparatus which is capable of evaluating the release of drug triamcinolone acetonide and bioadhesive properties of buccal tablets. The results produced by this apparatus concur with the predicted patterns.

**FIP (1997)**\(^6^4\) International pharmaceutical federation guidelines for dissolution testing of solid oral products were given by joint report of the section for official laboratories and medicines control services and the section of industrial pharmacists of the International pharmaceutical federation regarding the dissolution testing of solid oral immediate release products.

Siewert *et al.*, (2003)\(^6^5\) reviewed International pharmaceutical federation / American association of pharmaceutical scientists guidelines for dissolution/*in vitro* release testing of novel/special dosage forms. This article represented the scientific opinion of many experts and, in particular, is derived from a series of workshops held under the auspices of International pharmaceutical federation cosponsored by the Royal pharmaceutical society (UK), BPI colloquium pharmaceuticum (Germany), American association of pharmaceutical scientists (US) and the Food and drug administration (US).

**Fortunato (2005)**\(^6^6\) reviewed dissolution method development for immediate release solid oral dosage forms and suggested that the greatest challenge for the dissolution scientist occurs when poor results are obtained with these early batches, if suspect or poor results are observed from early batches, If dissolution results do not improve after all these trials, the dissolution scientist must not hesitate to inform the early phase development teams that future formulations may need to follow a different path.
Wei and Lobenberg, (2006)\textsuperscript{67} reported bio-relevant dissolution media as a predictive tool for glyburide as class II drug to predict the oral absorption of glyburide. The results revealed that BCS based parameters combined with software simulations can be used to establish an IVIVC for glyburide and \textit{in vitro/in silico} tools can potentially be used as surrogate for bioequivalence studies.

Vaghela \textit{et al.}, (2011)\textsuperscript{68} reviewed the development and validation of dissolution procedures. Dissolution test is required to study the drug release from the dosage form and its \textit{in vivo} performance. They highlighted development and validation of dissolution procedures had paramount importance during development of new formulation and in quality control. They also reviewed the development and validation of dissolution procedure(s) and to provide practical approaches for determining specificity, linearity, range, accuracy, precision, limit of detection, limit of quantitation and robustness and suggested that methods must be developed and validated not just for the dissolution test procedure itself, but also for any assay used to evaluate the test results.

Kulkarni \textit{et al.}, (2012)\textsuperscript{69} reported the developed and validated a dissolution test for pioglitazone hydrochloride tablets, containing 15 mg of active pharmaceutical ingredient, a frequently prescribed anti-diabetic, which had no dissolution assay in official monographs. They developed dissolution adequate for its purpose and can be applied for the quality control of 15 mg pioglitazone hydrochloride tablets.

Wang \textit{et al.}, (2012)\textsuperscript{70} developed an integrating chemical profiling approach and self reference strategy for the purpose of dissolution test of herbal medicines. They demonstrated that chromatographic fingerprints of the self-reference samples were translated by principal component analysis (PCA) into chemical profiles that highly correlate to their nominal gross concentrations in spite of the poor quantitative performances of some individual peaks with an example of \textit{ginkgo biloba} tablets. The developed method has potentials to enable deep insight into the molecular diffusion and dissolution of complex herbal formulations, and opened a new window to comprehensively consider the bioavailable properties of herbal medicines.
3.4. Method development

Verma and Joshi et al., (2006)\textsuperscript{71} developed simple, precise, rapid, selective and cost effective simultaneous HPTLC method for curcumin, piperine and thymol in an ayurvedic formulation using mobile phase toluene, ethyl acetate and methanol (9, 1, 0.5 v/v) at Rf values of 0.23, 0.30 and 0.64 whereas recovery was 100.41, 99.52 and 101.21% respectively for three components.

Zhou et al., (2009)\textsuperscript{72} reviewed advances in analysing herbal medicines by liquid chromatography coupled to time-of-flight mass spectrometry. The authors noted that the advantages of time-of-flight (TOF) MS such as accurate mass measurements and high resolution were very much applicable in the qualitative applications of herbal medicines with multi components complex herbal matrices. The main features of this review article is to throw light on potential applications of TOF which include quadrupole and ion trap TOF (QTOF and IT-TOF), hyphenated to LC for chemical analysis in HMs or HM-treated biological samples. Even minor details such as applied stationary phase, mobile-phase selection, accurate mass measurements, fragmentation and selectivity with their advantages and limitations for qualitative and quantification of herbal medicines was well highlighted.

Krishnaveni et al., (2009)\textsuperscript{73} developed and validated a rapid and simple HPLC method for the simultaneous quantification of curcumin and piperine in food products. This developed method is suitable for routine analysis of curcumin and piperine in food products.

Moorkoth et al., (2013)\textsuperscript{74} developed and validated an accurate, precise, reproducible, robust and linear stability indicating analytical method for estimation of Lafutidine in tablet dosage form by reverse phase HPLC method with the use of a UV detector. The developed method has its applicability in stability indicating assay under varied stress conditions such as oxidative, acid and alkaline stress conditions. The method was able to quantify degradation products in stress conditions.
3.5. Nanoparticles

Chen et al., (2003)\textsuperscript{75} prepared and characterized solution enhanced dispersion by supercritical CO\textsubscript{2} (SEDS) to prepare fine particles of puerarin. An organic nonsolvent, dichloromethane was employed in the process of solution-enhanced dispersion by supercritical CO\textsubscript{2} (SEDS) to prepare fine particles of puerarin. The SEDS process combined with the addition of dichloromethane could produce puerarin nanoparticles without contamination. The results in this study demonstrated that adding an organic nonsolvent in the SEDS process was effective in producing smaller fine particles and reducing the usage of CO\textsubscript{2}.

Shaikh et al., (2009)\textsuperscript{76} reported that nanoparticle encapsulation improves oral bioavailability of curcumin by at least 9-fold when compared to curcumin administered with piperine as absorption enhancer. The results clearly indicate the promise of nanoparticles for oral delivery of poorly bioavailable molecules like curcumin.

Li et al., (2009)\textsuperscript{77} described enhancement of gastrointestinal absorption of quercetin by solid lipid nanoparticles. Quercetin-loaded solid lipid nanoparticles (QT-SLN) were designed and characterized to evaluate the potential of using solid lipid nanoparticles (SLN) as an oral delivery carrier for poorly water soluble drugs. The authors highlighted that SLN were valuable as an oral delivery carriers to enhance the absorption of a poorly water soluble drug, quercetin.

Mansouri et al., (2011)\textsuperscript{78} prepared and characterized ibuprofen nanocrystals by solvent/antisolvent method. The prepared nano drug showed accelerated dissolution rate in water solvent.

Ekambaram et al., (2012)\textsuperscript{79} reviewed that solid lipid nanoparticles (SLN) are at the forefront of the rapidly developing field of nanotechnology with several potential applications in drug delivery and research. This review presented a broad treatment of solid lipid nanoparticles discussing their aims, production procedures, advantages, limitations and their possible remedies. The authors highlighted appropriate analytical techniques for characterization of SLN like photon correlation spectroscopy, scanning
electron microscopy, differential scanning calorimetry. Aspects of SLN route of administration and the in vivo fate of the carriers were also discussed.

Moorthi and Kathiresan, (2012)\textsuperscript{80} developed a combination i.e curcumin–piperine, or curcumin–quercetin or curcumin–silibinin drug-loaded nanoparticulate combination therapy for targeting and to revert multi drug resistant cancer. This study revealed that the developed combination prevented rapid systemic clearance, intestinal and hepatic metabolism, increased the aqueous solubility, enhanced bioavailability, targeted cancer cells and produced synergistic anti-cancer effect.

3.6. Pharmacokinetics

Prerana S et al., (2009)\textsuperscript{81} developed and validated RP-HPLC method for simultaneous determination of curcumin and piperine in human plasma for application in clinical pharmacological studies in view of the potential therapeutic application of curcumin and piperine in various diseases. The method was applied to the determination of the concentrations of curcumin and piperine in healthy volunteers after treatment with 1500 mg curcumin and 500 mg piperine, and should find an application in pharmacokinetic studies of these compounds.

Akram et al., (2010)\textsuperscript{82} reviewed properties, chemical constituents, pharmacokinetics and all possible mechanisms of action of curcumin derived from the rhizomes of \textit{curcuma longa} potential therapeutic effects including anti-oxidant, hepatoprotective, anti-inflammatory, anti-carcinogenic, anti-microbial, cardiovascular and gastrointestinal effects.