INTRODUCTION

Oral drug administration still remains the route of choice for the majority of clinical applications. Some drugs have ideal characteristics for good absorption to occur throughout the gastrointestinal tract, whereas others present difficulties. The biopharmaceutical Classification System, introduced by the Food and Drug Administration (FDA) in 1995\(^1\), has categorized drug in term of their solubility, (dissolution rate) and intestinal permeability. Class I compounds are defined as those with high permeability and high solubility, and are predicted to be well absorbed when given orally. All other compounds (Class II-IV) suffer from low solubility, low permeability or both, and will present challenges to the development of products with acceptable oral bioavailabilities\(^2\). An increasing no of new chemical entities are to be found in Classes II- IV and many of these display variable absorption in different region of the human GI tract\(^3\).

However, the major challenge with the design of oral dosage forms lies with their poor bioavailability. The oral bioavailability depends on several factors including aqueous solubility, drug permeability, dissolution rate, first-pass metabolism, presystemic metabolism, and susceptibility to efflux mechanisms. The most frequent causes of low oral bioavailability are attributed to poor solubility and low permeability\(^2,3\).

Solubility is one of the important parameters to achieve desired concentration of drug in systemic circulation for achieving required pharmacological response\(^4\). Poorly water soluble drugs often require high doses in order to reach therapeutic plasma concentrations after oral administration\(^5,7\). Low aqueous solubility is the major problem encountered with formulation development of new chemical entities as well as generic development. Any drug to be absorbed must be present in the form of an aqueous solution at the site of absorption. Water is the solvent of choice for liquid pharmaceutical formulations. Most of the drugs are either weakly acidic or weakly basic having poor aqueous solubility\(^8\).

The improvement of drug solubility thereby its oral bioavailability remains one of the most challenging aspects of drug development process especially for oral-drug delivery system. There are numerous approaches available and...
reported in literature to enhance the solubility of poorly water-soluble drugs. The techniques are chosen on the basis of certain aspects such as properties of drug under consideration, nature of excipients to be selected, and nature of intended dosage form\textsuperscript{9,10}. 

Previously, various delivery systems were used to enhance the solubility, dissolution and subsequently oral BA of poorly water soluble drugs. These systems mainly developed based on the micronization technique such as solid dispersions\textsuperscript{11-13}, inclusion complexes\textsuperscript{14}, liquid solid compacts\textsuperscript{15,16}, suspensions end emulsions\textsuperscript{17}. Different group of researchers also reported the various delivery systems developed for the enhancement of particular drugs examples include, zaleplon\textsuperscript{18} and candesartan cilexetil\textsuperscript{19}.

In this review, we provide the various novel delivery systems developed for the enhancement of oral BA by enhancing solubility, stability, bypassing metabolism using nano delivery systems such as lipid nanoparticles and self-emulsifying delivery systems. Consequence, enhancing the drug release for prolonged and sustained delivery using buccal\textsuperscript{20}, gastro retentive\textsuperscript{21} and modified release dosage forms in the forms such as osmotic delivery\textsuperscript{22,23}, sustained delivery\textsuperscript{24} and nano drug delivery systems\textsuperscript{25}.

**Dosage form related factors affecting bioavailability**

Both physiological components and physiochemical attributes of the drugs impact oral bioavailability of therapeutics. Be that as it may, the sort and attributes of the measurements shape in which the drug is incorporated can likewise crucially affect the bioavailability of the drug. For instance, the measure of drug achieving the blood can be finely regulated by the utilization of novel delivery systems. As of now, delivery systems have been developed to enhance the bioavailability of inadequately soluble drugs.

**Buccal delivery systems**

Buccal delivery has been developed to permit the prolonged localized therapy and improved systemic delivery and further to reduce the stability issues of drugs\textsuperscript{27}. The buccal mucosa responsible to avoiding first-pass metabolism effect is a frightening barrier to drug absorption and dissolution, especially for poorly bioavailable drugs with low dose biopharmaceutical and also arising from the recent advances in genomics and proteomics\textsuperscript{28}. The buccal route is typically used for extended drug delivery, so formulations that can be attached to the buccal mucosa are favored. The bioadhesive polymers used in buccal drug delivery to retain a formulation are typically hydrophilic macro-molecules containing numerous hydrogen bonding groups. Newer second-generation bioadhesives have been developed and these include modified or new polymers that allow enhanced adhesion and/or drug delivery, in addition to site-specific ligands such as lectins\textsuperscript{29}. Over the last 20 years a wide range of formulations has been developed for buccal drug delivery (tablet, patch, liquids and semisolids) but comparatively few have found their way onto the market. As of now, this course is confined to the transport of a predetermined number of small lipophilic drugs that promptly cross the buccal mucosa. Be that as it may, this delivery could turn into an enormous means for the delivery of a scope of researchers in the coming years, if the boundaries to buccal medication delivery are overcome\textsuperscript{30}.

The oral bioavailability of domperidone was enhanced by using buccal patches\textsuperscript{30}. Further, a comparative study of domperidone buccal films was observed using hot melt extrusion technique\textsuperscript{31}. The enhancement of pioglitazone and felodipine oral bioavailability in the combined dosage form was noticed with buccal pellets. Buccal pellets of these systems were developed by using response surface methodology with hot melt extrusion technology\textsuperscript{32}. From the same group of researchers, the enhancement of oral bioavailability of promethazine hydrochloride was observed with buccal patches\textsuperscript{33}. Buccal delivery of omeprazole, pranopanolol, flurbiprofen, carvedilol, nimodipine, atenolol and pravastatin\textsuperscript{34-41}.

**Gastro retentive delivery systems**

Gastro retentive dosage forms are drug delivery systems which remain in the stomach for an extended period of time and allow both spatial and time control of drug liberation. Basically gastro retentive systems swells following ingestion and is retained in the stomach for a number of hours, while it continuously releases the incorporated drug at a controlled rate to preferred absorption sites in the upper intestinal tract. Their application can be advantageous in the case of drugs absorbed mainly from the upper part of GIT or are unstable in the medium of distal intestinal regions. They can also be used beneficially in the local therapy of the stomach\textsuperscript{42,43}. Various attempts have been made to retain the dosage form in the stomach as a way of increasing the retention time. These attempts include introducing floating dosage forms (gas generating systems, swelling and expanding systems, mucoadhesive, high density systems, modified shape systems, gastric emptying delaying devices and co-administration of gastric delaying drugs\textsuperscript{44}. Among these, the floating dosage forms have been used most commonly.

Narendra et al. developed the floating matrix tablets of levofloxacin hydrochloride to improve the bioavailability\textsuperscript{45}. From the in vivo radiographic studies, the mean residence time of optimized floating tablets showed more than 4 h in fasting conditions in healthy human volunteers. Reddy et al. reported the improved gastric residence time of floating matrix tablet of ofloxacin and ornidazole in combined dosage form\textsuperscript{46}. The floating matrix tablets were prepared by direct compression method using hydrophilic polymers.

Floating matrix tablets of cefixime trihydrate was developed and showed enhancement in relative bioavailability of optimized formulation was 1.61-fold when compared to conventional formulation\textsuperscript{47}. Mucoadhesive floating tablets of riserdronate sodium was developed using central composite design and evaluated for in vivo imaging behavior. From the results, the mean residence time was more than 4 h and exhibited better gastric adhesive property\textsuperscript{48}.

Mucoadhesive floating matrix tablets of amoxycillin trihydrate for the eradication of $H. pylori$ were developed\textsuperscript{49}. The floating mini tablets of clarithromycin was developed and evaluated with modified dissolution apparatus\textsuperscript{50}. Floating matrix tablets of quetiapine fumarate was prepared and noticed for enhanced drug release rate upto 12 h\textsuperscript{51}.

**Nano formulations**

Among different ways to deal with enhance the oral bioavailability of small drugs and biopharmaceuticals, nanotechnologies have appeared to be extremely encouraging. Diverse nanotechnology delivery systems have demonstrated the possibility to facilitate oral transport by overcoming to some degree at least one of the previously mentioned challenges displayed by the oral route of administration.
The nano formulations, especially lipid nanocarriers such as solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), self-emulsifying drug delivery systems (SEDDS) and liposomes are well known ones.

SLNs and NLCs are sub-micron colloidal carrier systems, particle size range from 50-1000 nm. SLNs are made up of solid lipid, which are available as solids at room temperature. SLNs are used as vehicle for oral delivery and topical delivery, intra nasal delivery, transdermal delivery and ocular delivery of various drugs. NLCs are modified form of SLNs, in which one part of the solid lipid is replaced with liquid lipid. The advantage of NLCs over SLNs was enhance the drug loading and reduces the drug expulsion from the lipid matrix.

SLNs and NLCs enhance the BA of poorly water soluble drugs. The enhanced BA of drugs from the SLNs might be including one of the following; virtue of small particle size which provides the effective surface area; presence of triglycerides facilitates the lymphatic uptake and by pass the presystemic metabolism; the use of surfactants in the SLNs formation, promotes the surface area as well as gastric motility.

Kishan and team extensively involved in the research of SLNs especially for antihypertensive drugs namely nisoldipine (2.3 folds), candesartan cilexetil (2.75 folds), felodipine (2.2 folds), lacidipine (2 folds) and olmesartan medoxomil were reported. They also develop and report the enhanced oral BA of rosuvastatin calcium, quetiapine fumarate and loaded SLNs. Further, comparative pharmacokinetic studies of olmesartan with nanosuspensions were reported and SLNs exhibited higher BA than nanosuspension. Similar reports were observed with nanosuspension of olmesartan.

SLNs also used for the development of oral delivery of anticancer drugs such as capetabine for colon cancer, camptothecin for ovarian cancer were reported. The oral BA of zaleplon also enhanced by SLNs approach. Similarly, oral BA of another antipsychotic drug Zotepine was improved by both SLN and NLC systems. The pharmacodynamic activity of orally administered drugs was also enhanced by the SLNs delivery systems. These were observed with candesartan, nisoldipine, rosuvastatin calcium and isradipine.

NLCs of nisoldipine also developed and compared with SLNs and exhibited almost equal enhancement in the oral BA. Candesartan cilexetil, olmesartan medoxomil loaded NLCs were developed and exhibited enhanced oral BA.

SEDDS are isotropic blends of oils, surfactants, solvents and co-solvents/surfactants, can be utilized for the outline of definitions with a specific end goal to enhance the oral absorption of lipophilic drugs. SEDDS can be orally directed in soft or hard gelatin shells and enclose fine generally stable oil–in–water (o/w) emulsions upon watery weakening inferable from the delicate disturbance of the gastrointestinal liquids. The productivity of oral ingestion of the medication compound from the SEDDS relies upon numerous formulation–related parameters, for example, surfactant fixation, oil/surfactant proportion, and extremity of the emulsion, bead size and charge, all of which basically decide the self-emulsification capacity. Therefore, just unmistakable pharmaceutical excipient blends will prompt proficient self-emulsifying frameworks.

Albeit numerous investigations have been completed, there are few medication items on the pharmaceutical market figured as SEDDS affirming the trouble of planning hydrophobic medicinal mixes into such details. At exhibit, there are four medication items, Sandimmune® and Sandimmun Neoral® (cyclosporin A), Norvir® (ritonavir), and Fortovase® (saquinavir) on the pharmaceutical market, the dynamic mixes of which have been figured into particular SEDDS.

Oral bioavailability of lercanidipine was improved by SEDDS approach. SEDDS of lercanidipine was prepared and converted to powder form. The powder form of SEDDS was found to be stable at room temperature and refrigerated temperature. From the results, enhancement in the dissolution rate was observed with powdered form of SEDDS than SEDDS alone.

Various other delivery systems such as chronomodulated nanoemulsions, colon delivery, nanocrystals and cubosomes were reported and SLNs exhibited higher BA than nanosuspension. Similar reports were observed with nanosuspension of olmesartan.

SLNs also used for the development of oral delivery of antidepressants such as Wellbutrin, (buprofezin) for depressive disorder, SEDDS of doxepin, lacidipine, candesartan cilexetil, felodipine and olmesartan medoxomil were reported. They also develop and report the enhanced oral BA of rosuvastatin calcium, quetiapine fumarate and loaded SLNs. Further, comparative pharmacokinetic studies of olmesartan with nanosuspensions were reported and SLNs exhibited higher BA than nanosuspension. Similar reports were observed with nanosuspension of olmesartan.

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