Novel Delivery System Used for Oral Bioavailability Enhancement of Poorly Water Soluble Drugs

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Abstract

Majority of the drugs used for the treatment of various diseases are administered by oral route using conventional delivery. The major drawback of the oral administration is the poor bioavailability due to the poor water solubility, chemical stability and pre-systemic metabolism. Numerous researches are going on for the improvement of oral bioavailability of drugs using novel drug delivery systems as an alternative to conventional delivery systems. Majority of the novel delivery system includes; solid dispersion, sustained, controlled buccal, gastro retentive, nano carrier delivery systems such as lipid nanoparticles, and self-emulsifying systems. The oral bioavailability improvement by these delivery systems might be due to the increased particle size, improved dissolution and/or permeation and subsequently bioavailability of the drugs. In this review, we attempt to discuss the various novel delivery systems developed for the enhancement of oral bioavailability of poorly water soluble therapeutics.

Keywords: Oral bioavailability, poor solubility, stability, metabolism, novel delivery systems, nano carriers.

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 therapeutically useful plasma concentrations after oral administration\(^5,6\). 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.\(^9\)\(^{10}\)

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,\(^11\)\(^-\)\(^13\) indusion complexes,\(^14\) liquid solid compacts,\(^15\) \(^16\) suspensions,\(^17\) end emulsions. Different group of researchers also reported the various delivery systems developed for the enhancement of particular drugs examples include, zaleplon\(^18\) and candesartan cilexetil\(^19\).

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. Consequently, enhancing the drug release for prolonged and sustained delivery using buccal\(^20\), gastro retentive\(^21\) and modified release dosage forms in the forms such as osmotic delivery,\(^22\)\(^23\) sustained delivery,\(^25\) and nano drug delivery systems.\(^26\)

**Dosage form related factors affecting bioavailability**

Both physiological components and physicochemical 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.\(^27\) 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.\(^28\) 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.\(^29\) 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.\(^30\)

The oral bioavailability of domperidone was enhanced by using buccal patches.\(^31\) Further, a comparative study of domperidone buccal films was observed using hot melt extrusion technique.\(^32\) 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.\(^33\) From the same group of researchers, the enhancement of oral bioavailability of promethazine hydrochloride was observed with buccal patches.\(^34\) Buccal delivery of omeprazole, propranolol, flurbiprofen, carvedilol, nimodipine, atenolol and pravastatin.\(^35\)\(^-\)\(^37\)

**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.\(^38\)\(^39\) 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).\(^40\) 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.\(^41\) 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.\(^42\) The floating matrix tablets were prepared by direct compression method using hydrophilic polymers.

Floating matrix tablets of cefixime trihydrate were developed and showed enhancement in relative bioavailability of optimized formulation was 1.61-fold when compared to conventional formulation.\(^43\) Mucoadhesive floating tablets of risendronate 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.\(^44\)

Mucoadhesive floating matrix tablets of amoxyclillin trihydrate for the eradication of *H. pylori* were developed.\(^45\) The floating mini tablets of clarithromycin was developed\(^46\) and evaluated with modified dissolution apparatus.\(^47\) Floating matrix tablets of quetiapine fumarate was prepared and noticed for enhanced drug release rate up to 12 h.\(^48\)

**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.

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**References**

1. Lakavath et al. (2020) Journal of Drug Delivery & Therapeutics. 10(6-s):139-144

2. Journal of Drug Delivery & Therapeutics. 10(6-s):139-144

3. CODEN (USA): JDDTAO

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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 cilexelit (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 and olmesartan medoxomil were reported. They also develop and report the enhanced oral BA of rosuvastatin calcium and olmesartan medoxomil were reported. Further, comparative pharmacokinetic studies of olmesartan with nano suspensions were reported and SLNs exhibited higher BA than non suspension. Similar reports were observed with nano suspensions of olmesartan.

SLNs also used for the development of oral delivery of anticancer drugs such as capetitabine 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 cilexelit, 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 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, head size and charge, all of which basically decide the self-emulsification capacity. Therefore, just unmistakable pharmaceutical expipient 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 affining the trouble of planning hypodermic medication 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, nanoeumulsions, column delivery, nanocrystals and cubosomes are modified form of delivery systems. These systems are utilized for the outline of poorly water soluble drugs. To complete development works within a limited amount of time, the establishment of a suitable formulation strategy should be a key consideration for the pharmaceutical development of poorly water-soluble drugs.

**References**

1. Food and Drug Administration. (2000). Guidance for industry: waiver of in vivo bioavailability and bioequivalence studies for immediate-release solid oral dosage forms based on a biopharmaceutics classification system. Food and Drug Administration, Rockville, MD.
2. Amidon, G. L., Lennernäs, H., Shah, V. P., & Crison, J. R. A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. *Pharmaceutical Research*, 1995; 12(3):413-420.
3. Broccatelli, F., Cruciani, G., Benet, L. Z., & Oprea, T. I. BDQCS class prediction for new molecular entities. *Molecular Pharmaceutics*, 2012; 9(3):570-580.
4. Reddy, B. B. K., & Karunakar, A. Biopharmaceutics classification systems: a regulatory approach. *Dissoilation Technologies*, 2011; IQ(1):31-37.
5. Duddhipala N. A Comprehensive Review on Solid Lipid Nanoparticles as Delivery Vehicle for Enhanced Pharmacokinetic and Pharmacodynamic Activity of Poorly Soluble Drugs. Int J Pharm Sci Nanotech. 2019; 12:4421-46.
6. Kumar A, Sahoo SK, Padhee K, Kochar PS, Sathapathy A, Pathak N. Review on solubility enhancement techniques for hydrophobic drugs. *Pharmacie Globale*. 2011; 3(3):601-7.
7. Duddhipala N. Influence of Solid Lipid Nanoparticles on Pharmacodynamic Activity of Poorly Oral Bioavailable Drugs. *International Journal of Pharmaceutical Sciences and Nanotechnology*. 2020 Jul 11; 13(4):4979-83.
14. Palem CR, Reddy ND, Sathyarayana G, Varsha BP. Development and optimization of Atorvastatin calcium-cycloexedrin inclusion complexed oral disintegrating tablets for enhancement of solubility, dissolution, pharmacokinetic and pharmacodynamic activity by central composite design. Int J Pharm Sci Nanotech. 2016; 9(1):1-8.

15. Chella N, Shastri N, Talakadkanna RR. Use of the liposoluble compact technique and dissolution improvement for the dissolution rate of valsartan. Acta Pharmaceutica Sinica B. 2012 Oct 1; 3(4):502-8.

16. Butreddy D., Dhuppal D. Enhancement of solubility and dissolution rate of trandolapril sustained release matrix tablets by liposoluble compact approach. Asian Journal of Pharmaceutics• Oct-Dec. 2015; 9(4):1.

17. Allegra JR, Hawkey SA. Attenuation of sound in suspensions and emulsions: Theory and experiments. The Journal of the Acoustical Society of America. 1972 May; 51(5B):154-65.

18. Dhuppal D., N. A Review of Novel Formulation Strategies to Enhance Oral Delivery of Zaleplon. J Bioeq Availab. 2016; 8(211-213).

19. Narendar D and Kishan V. Candesartan cilexetil nanoparticles for improved oral bioavailability. Ther del. 2017; 8(2):79-88.

20. Peddappalli H, Dhuppal D, Chinnala KM, Banala N. Transmucosal Delivery of Duloxetine Hydrochloride for Prolonged Release: Preparation, in vitro, ex vivo Characterization and in vitro-ex vivo Correlation. Int J Pharm Sci Nanotech. 2016; 11(5):29-4258.

21. Sathish D., Himabindu S., Shravan, Y., & Madhusudan, R.Y. Floating drug delivery systems for prolonging gastric residence time: a review. Current drug deli. 2011; 8(5):494-510.

22. Donthi MR, Dhuppal N, Komalla DR, Suram D, Banala N. Design and Evaluation of Floating Multi Unit Mini Tablets (MUMTS) Muco Adhesives Drug Delivery System of Famotidine to Treat Upper Gastro Intestinal Ulcers. Journal of Pharmocovigilance. 2015 Oct 12.

23. Arjun, N, Narendar, D, Sunita, K, Harika, K, Madhusudan, R.Y., & Nagaraj, B. Development, evaluation and influence of formulation and process variables on in vitro performance of oral elementary osmotic device of atenolol. Int J Pharm Invest, 2016; 6(4):1-9.

24. Narendar, D., Arjun, N, Sunita, K, Harika, K, & Nagaraj, B. Development of osmotically controlled oral drug delivery systems of tramadol hydrochloride: effect of formulation variables on in-vitro release kinetics. Asian J Pharm. 2016; 10(3):31-10.

25. Sunil, R, Pavan, KP, Narendar, D., & Madhusudan, R. Y. Development and in vitro evaluation of modified release coated tablets of freely water soluble drug metropolon succinate. American J Pharm Tech Res. 2012; 2(3):1-15.

26. Nagaraj, B., Nareana, D, Sushma P. Formulation and evaluation of microemulsion-based transdermal delivery of duloxetine hydrochloride. International Journal of Pharmaceutical Sciences and Nanotechnology. 2020 Jan 31; 13(1):4773-82.

27. Rao, M.Y., Vanu, G., & Charly, B.R. Design and evaluation of mucoadhesive drug delivery systems. Indian Drugs. 1998; 35:558-65.

28. Smart, J.D. Buccal drug delivery. Expert Opin Drug Deliv. 2005; 2(3):507-17.

29. Mahalapreedy D, Narendar D, Devendhar K, Dinesh S, Kiran S, Nagaraj B. Preparation and evaluation of ketoconazole enteric coated mini tablets for prevention of chronic inflammatory disease. J Pharm Drug Deliv Res. 2015; 4(2).

30. Reddy, P.C., Chaitanya, K.S., & Madhusudan, R.Y. A review on bioadhesive buccal drug delivery systems: current status of formulation and evaluation methods. Daru, 2011; 19(6):385-403.

31. Palem, C.R., Gannu, R, Doodipala, N., Yamsani, V., & Yamsani, M.R. Transmucosal delivery of domperidone from bilayered buccal patches: in vitro, ex vivo and in vivo characterization. Archives of pharmacal research, 2011 34(10):1701-1710.

32. Palem, C.R., Dhuppal D, N.R., Battu, S.K., Repka, M.A., & Rao Yamsani, M. Development, optimization and in vivo characterization of domperidone-controlled release heat-melt-extruded films for buccal delivery. Drug development and industrial pharmacy, 2016; 42(3):473-484.

33. Palem, C.R., Dhuppal D., Battu, S.K, Goda, S, Repka, M.A., & Yamsani, M. R. Combined dosage form of pioglitazone and felodipine as mucoadhesive pellets via hot melt extrusion for improved buccal delivery with application of quality by design approach. Journal of Drug Delivery Science and Technology, 2015; 30:209-219.

34. Choppaparu C, Palem CR, Yamsani MR. Development of Promethazine mucoadhesive tablets for buccal delivery: in vitro, ex-vivo and in vivo characterization. American J PharmTech Res. 2012; 21(1):169-705.

35. Choi, H. G., & Kim, C. K. Development of omeprazole buccal adhesive tablets with stability enhancement in human saliva. Journal of controlled release, 2000; 68(3):397-404.

36. Raghuraman, S, Venrajan, G, Ravi, Jeyabalana, B, Johnson, D. B., & Sankar, V. Design and evaluation of propranolol hydrochloride buccal films. Indian journal of pharmacological sciences, 2002; 64(1):32.

37. Perioli, L, Ambrogvio, V, Stefano, G, Ricci, M, Blasi, P, & Carlo, R. Mucoadhesive bilayered tablets for buccal sustained release of flurbiprofen. AAPS PharmSciTech. 2007; 8(3):E20–E27.

38. Yamsani, V.Y., Ramesh, G., Chandrasekh. N., Ali, M., & Ali, J. Novel buccal adhesive system for anti-hypertensive agent nimodipine. Pharm Dev Technol, 2010; 15(2):124-30.

39. Surya, R. N.A., Bhabani, S.N, Amit, K. N., & Bivarwanjan, M. Formulation and evaluation of buccal patches for delivery of atenolol. AAPS PharmSciTech, 2010; 11(3):1038-1044.

40. Shindhaye, S.S., Thakkar, P.V.D., & Kadak, V.J. Buccal drug delivery of pravastatin sodium. AAPS PharmSciTech, 2010; 11:416-24.

41. Streubel, A., Steppmann, J., & Bodmeier, R. (2006). Gastroretentive drug delivery systems. Expert Opin Drug Deliv, 3(2), 217-33.

42. Donthi MR, Dhuppal NR, Komalla DR, Suram D, Banala N. Preparation and Evaluation of Fixed Combination of Ketoprofen Enteric Coated and Famotidine Floating Mini Tablets by Single Unit Encapsulation System. Journal of Bioequivalence & Bioavailability, 2015; 7(6):279.

43. Carla, M.L., Catarina, B, Alessandra, R., & Francesca, B. Overview on gastro retentive drug delivery systems for improving drug bioavailability. Int J Pharm, 2016; 50(1):144-158.

44. Narendar, D, Palem, C.R, Reddy, S., & Rao, Y.M. Pharmaceutical development and clinical pharmacokinetic evaluation of gastroretentive floating matrix tablets of levofloxacin. Int J Pharma Sci and Nanotech, 2011; 4(3):1461-1467.

45. Reddy, N.D., Chinnia R. P., Sunil, R., & Madhusudan, R. Y. Development of floating matrix tablets of Olfoxacin and Ornidazole in combined dosage form: in vitro and in vivo evaluation in healthy human volunteers. Int J Drug Deli, 2012; 4:462-469.

46. Ramesh, B., & Kishan, V. Development of gastroretentive drug delivery system for cefuroxime axetil: In vitro and In vivo evaluation, Pharma Develop and Tech. 2013; 18(5):1230-1237.

47. Ramesh, B., & Kishan, V. Statistical optimization of floating bioadhesive drug delivery system for risedronate sodium: In vitro, ex vivo and In vivo evaluation. Int J of Drug deli. 2014; 6:36-49.
49. Narendar, D., Arjun, N., Karthik, Y. J., & Ramesh, B. Amoxyccillin trihydrate floating bioadhesive drug delivery system for eradication of helicobacter pylori: preparation, in vitro and ex vivo evaluation. J Bioeng. 2016; 8(3):118-124.

50. Arun, B. R., & Narendar, D. Development of multiple-unit floating drug delivery system of clarithromycin: formulation, in vitro dissolution by modified dissolution apparatus, in vivo radiographic studies in human volunteers. Drug res. 2017; 67:412-418.

51. Narendar, D., Someshwara, K., Arjun, N., & Madhusudan R.Y. Quality by design approach for development and optimization of Quetiapine Fumarate effervescent floating matrix tablets for improved oral delivery. J Pharm Invest. 2016; 46(3):23-263.

52. Müller, R.H., Mäder, K., & Gohla, S. Solid lipid nanoparticles (SLN) for controlled drug delivery – a review of the state of the art. Eur J Pharm Biopharm. 2000; 50(1):161-177.

53. Unér, M., & Yener, G. Importance of solid lipid nanoparticles (SLN) in various administration routes and future perspectives. Int J Nanomed. 2007; 2(3):289-300.

54. Narendar, Duddhipala, Arjun, Narala, & Ramesh, Bomma. Recent updates in the formulation strategies to enhance the bioavailability of drugs administered via intranasal route. J bioeng. avail. 2016; 5(5):204-207.

55. Duddhipala N., Ahmed AAY, Nagaraj B. Colloidal lipid nanodispersion enriched hydrogel of anti fungal agent for management of fungal infections: comparative in vitro, ex vivo and in vivo evaluation for oral and topical application. Chemisty and Physics of Lipids. 2020: 104981.

56. Souto EB, Baklim I, Oliveira WP, Rao R, Yadav N, Gama FM, Mahant S. SLN and NLC for topical, dermal, and transdermal drug delivery. Expert Opinion on Drug Delivery. 2020 Mar 3; 17(3):357-77.

57. Narendar D, Thirupathi G. Neuroprotective effect of ropinirole loaded lipid nanoparticles hydrgol for Parkinson’s disease: preparation, in vitro, ex vivo, pharmacokinetic and pharmacodynamic evaluation. Pharmaceutics. 2020; 12(5):448.

58. Duddhipala N. Polymeric Matrices at Micro and Nanoscale for Ocular Drug Delivery. Saudi J of Biomed Res. 2017; 2:96-100.

59. Akshaya Tatke, Narendar Duddhipala, Karthik Yadav Janga, Sai Prachetan Balguri, Bharathi Avula, Monica M. Jablonski Soumyajit Majumdar. In-Situ Gel of Triamcinolone Acetonide-Loaded Solid Lipid Nanoparticles for Improved Topical Oral Delivery: Tear Kinetics and Ocular Disposition Studies. Nanomaterials (Basel). 2018 Dec 27; 9(1). pii: E33. doi: 10.3390/nnano9010033.

60. Reddy, N.D. Ocular Iontophoresis for Anterior and Posterior Segment Drug Delivery. Saudi Pharm Sci. 2017; 3(84):853-857.

61. Müller, R.H., Radtke, M., & Wissing, S.A. Solid lipid nanoparticles (SLN) and nanostructured lipider carriers (NLC) in cosmetic and dermatological preparations. Adv Drug Deliv Rev. 2002; 54:811-835.

62. Ahmed AAY, Narendar D, Mujumdar S. Ciprofloxacin Loaded Nanostructured Lipid Carriers Incorporated into In-Situ Gels to Improve Management of Bacterial Endophthalmitis. Pharmaceutics. 2020; 12(6):572.

63. Naseri N, Valzadeh H, Zakeri-Milani P. Solid lipid nanoparticles and nanostructured lipid carriers: structure, preparation and application. Advanced pharmaceutical bulletin. 2015 Sep; 5(3):305.

64. Duddhipala N, Ahmed AA. Amelioration of ketoconazole in lipid nanoparticles for enhanced antifungal activity and bioavailability through oral administration for management of fungal infections. Chemistry and Physics of Lipids. 2020; 232:104953.

65. Priano L, Esposti D, Esposti R, Castagna G, De Medici C, Fraschin F, Gasco MR, Mauro A. Solid lipid nanoparticles incorporating melatonin as new model for sustained oral and transdermal delivery systems. Journal of nanoscience and nanotechnology. 2007 Oct 1; 7(10):3596-601.

66. zur Mühlen A, Schwarz W, Mehnter W. Solid lipid nanoparticles (SLN) for controlled drug delivery–drug release and release mechanism. European journal of pharmacetics and biopharmaceutics. 1998 Mar 1; 45(2):149-55.

67. Narendar, D., & Kishan, V. Pharmacokinetic and pharmacodynamic studies of misoprostol-loaded solid lipid nanoparticles developed by central composite design. Drug Dev Ind Pharm. 2015; 41(12):1968-77.

68. Narendar, D., & Kishan, V. Candesartan cilexetil-loaded solid lipid nanoparticles for oral delivery: characterization, pharmacokinetic and pharmacodynamic evaluation. Drug Deli. 2016; 23(2):395-404.

69. Usma, G., Narendar, D., & Kishan, V. Preparation, characterization and in vivo evaluation of felodipine solid lipid nanoparticles to improve the oral bioavailability. Int J Pharma Sci Nanotech. 2015; 8(4):2995-3002.

70. Sandeep, V., Narendar, D., Arjun, N., & Kishan, V. Lacidipine loaded solid lipid nanoparticles for oral delivery: Preparation, characterization and in vivo evaluation. Int J Pharma Sci Nanotech. 2016; 9(6):3524-30.

71. Arun, B., Narendar, D., & Kishan, V. Development of olmesartan medoxomil lipid based nanoparticles and nanosuspension: preparation, characterization and comparative pharmacokinetic evaluation. Artificial cells, nanomed and biotech. 2018; 46(1):126-137.

72. Duddhipala, N., & Veerabrahma, K. Improved anti-hyperlipidemic activity of Rosuvastatin Calcium via lipid nanoparticles: Pharmacokinetic and pharmacodynamic evaluation. European Journal of Pharmacetics and Biopharmaceutics, 2017; 110:47-57.

73. Suvarna, G., Narendar, D., & Kishan, V. Preparation, characterization and in vivo evaluation of rosuvastatin calcium loaded solid lipid nanoparticles. Int J Pharma Sci Nanotech. 2015; 8(1):2779-2785.

74. Narala, A., & Veerabrahma, K. Preparation, characterization and evaluation of olmesartan medoxomil solid lipid nanoparticles to improve the oral bioavailability. Journal of pharmaceutics, 2013.

75. Nagaraj, K., Narendar, D., & Kishan, V. Development of olmesartan medoxomil optimized nanosuspension using Box-Behnken design to improve oral bioavailability. Drug Dev Ind Pharm, 2017; 43(7):1205-1214.

76. Duddhipala, N., & Puchchakayala, G. Cepacitabine lipid nanoparticles for anti-colon cancer activity in 1, 2-dimethylhydrazine induced colon cancer: Preparation, cytotoxic, pharmacokinetic and pathological evaluation. Drug development and industrial pharmacy, (just-accepted), 2018; 1-32.

77. Yang S, Zhu J, Lu Y, Liang B, Yang C. Body distribution of camptothecin solid lipid nanoparticles after oral administration. Pharmaceutical research. 1999 May 1; 16(5):751-7.

78. Duddhipala, N., & Janga, K. Y. Lipid nanoparticles of zaleplon for improved oral delivery by Box-Behnken design: optimization, in vitro and in vivo evaluation. Drug development and industrial pharmacy, 2017; 43(7):1205-1214.

79. Nagaraj B, Tirumalesh C, Dinesh S, Narendar D. Zotepine loaded lipid nanoparticles for oral delivery: development, characterization, and in vivo pharmacokinetic studies. Future Journal of Pharmaceutical Sciences. 2020 Dec 6(1):1-11.

80. Tirumalesh C, Suram D, Duddhipala N, Banala N. Enhanced pharmacokinetic activity of Zotepine via nanostructured lipid carrier system in Wistar rats for oral application. Pharmaceutical Nanotechnology. 2020 Apr 1; 8(2):148-60.

81. Thirupathi, G., Swetha, E., & Narendar, D. Role of isradipine loaded solid lipid nanoparticles in the pharmacodynamic effect of isradipine in rats. Drug res, 2017; 67(03):163-169.

82. Duddhipala, N., Janga, K. Y., & Gorre, T. Comparative study of niosilipid-loaded nanostructured lipid carriers and solid lipid nanoparticles for oral delivery: preparation, characterization, permeation and pharmacokinetic evaluation. Artificial cells, nanomedicine, and biotechnology, 2018; 1-10.

83. Paudel, A., Imam, S. S., Fazil, M., Khan, S., Hafeez, A., Ahmad, F. J., & Ali, A. Formulation and Optimization of Candesartan Cilexetil Nano Lipid Carrier: In Vitro and In Vivo Evaluation. Current drug delivery, 2017; 14(7):1005-1015.

84. Pathakwad, V., Dora, C. P., Kushwah, V., & Jain, S. Nanostructured lipid carriers of olmesartan medoxomil with enhanced oral bioavailability. Colloids and Surfaces B: Biointerfaces, 2017; 154:10-20.

85. Pouton CW. Formulation of self-emulsifying drug delivery systems. Advanced drug delivery reviews. 1997 Apr 14; 25(1):47-58.
86. Gursoy RN, Benita S. Self-emulsifying drug delivery systems (SEDDS) for improved oral delivery of lipophilic drugs. Biomedicine & pharmacotherapy. 2004 Apr 1; 58(3):173-82.
87. Krishna VM, Kumar VB, Dudhipala N. In-situ Intestinal absorption and pharmacokinetic investigations of carvedilol loaded supersaturated self-emulsifying drug system. Pharmaceutical nanotechnology. 2020 Jun 1; 8(3):207-24.
88. Tang JL, Sun J, He ZG. Self-emulsifying drug delivery systems: strategy for improving oral delivery of poorly soluble drugs. Current drug therapy. 2007 Jan 1; 2(1):85-93.
89. Kallakunta, V. R., Bandari, S., Jukanti, R., & Veerareddy, P. R. Oral self-emulsifying powder of lorcandipine hydrochloride: formulation and evaluation. Powder Technology, 2012; 221:375-382.
90. Alekya K, Narendar D, Arjun N, Mahipal D and Nagaraj B. Design and evaluation of chronomodulated drug delivery of tramadol hydrochloride. Drug res. 2017; Early online.
91. Yu H, Huang Q. Improving the oral bioavailability of curcumin using novel organogel-based nanoemulsions. Journal of agricultural and food chemistry. 2012 May 30; 60(21):5373-9.
92. Corinne Sweeney, Narendar Dudhipala, Ruchi Thakkar, Tabish Mehraj, Sushrut Marathe, Waseem Gul, Mahmoud. A. ElSohly, Brian Murphy, Soumyajit Majumdar. Effect of surfactant concentration and sterilization process on intraocular pressure-lowering activity of Δ9-tetrahydrocannabinolvaline-hemisuccinate (NB1111) nanoemulsions. Drug Delivery and Translational Research. 2020 https://doi.org/10.1007/s13346-020-00871-9.
93. Amidon S, Brown JR, Dave VS. Colon-targeted oral drug delivery systems: design trends and approaches. Aaps Pharmscitech. 2015 Aug 1; 16(4):731-41.
94. Rajitha R, Narendar D, Arjun N, Mahipal D and Nagaraj B. Colon delivery of naproxen: preparation, characterization and in vivo evaluation. IJPSN, 2016; 9(3):1-10.
95. Gao L, Liu G, Ma J, Wang X, Zhou L, Li X, Wang F. Application of drug nanocrystal technologies on oral drug delivery of poorly soluble drugs. Pharmaceutical research. 2013 Feb 1; 30(2):307-24.
96. Karri V, Butreddy A, Dudhipala N. Fabrication of Efavirenz Freeze Dried Nanocrystals: Formulation, Physicochemical Characterization, In Vitro and Ex Vivo Evaluation. Advanced Science, Engineering and Medicine. 2015 May 1; 7(5):385-92.
97. Karami Z, Hamidi M. Cubosomes: remarkable drug delivery potential. Drug discovery today. 2016 May 1; 21(5):789-801.
98. Butreddy A, Narala A, Dudhipala N. Formulation and characterization of Liquid Crystalline Hydrogel of Agomelatin: In vitro and Ex vivo evaluation. Journal of Applied Pharmaceutical Science. 2015 Sep; 5(09):110-4.