Recent development in novel drug delivery systems for delivery of herbal drugs: An updates

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GSC Advanced Research and Reviews, 2021, 08(02), 008–018

Publication history: Received on 22 June 2021; revised on 27 July 2021; accepted on 30 July 2021

Article DOI: https://doi.org/10.30574/gscarr.2021.8.2.0158

Abstract

In the recent years, herbal medicines have gained worldwide attention of peoples and researchers due to their esthetic value, more patient’s compliance and prominent therapeutic effects. Novel drug delivery systems for delivery of herbal drugs possesses several advantages over conventional formulations. It includes enhancement of solubility, bioavailability, and protection from toxicity, etc. The herbal drugs can be used in a more upright course with enhanced efficacy by incorporating them into suitable dosage forms. This can be achieved by designing novel drug delivery systems for such drugs. Such systems are polymeric nanoparticles, nanocapsules, phytosomes, animations, microsphere, etc. The present article highlights the current condition of the development of novel herbal formulations and summarizes their type of active components, biological activity, and applications of novel formulations.

Keywords: Novel Drug Delivery; Herbal drug; Nanoparticles; Liposome; Phytosome

1. Introduction

The use of herbal medicines has gain worldwide attention due to their esthetic value, more patient’s compliance and prominent therapeutic effects. Ethno-botanical information of such plants and their usage by indigenous cultures is useful in the conservation of traditional system of medicine, biodiversity, to promote health care system [1-2]. There are thousands of such types of plants widely available throughout the world. Such plants include, Withania somnifera, Aloe vera, Azadirachta indica, Murraya Koenigii, Carica papaya, Allium sativum, etc [3-17].

Novel drug delivery systems for delivery of herbal drugs possesses several advantages over conventional formulations [18]. An optimum amount of the concerned drug is administered to the patient in such a way that it reaches exactly the site of action’ and produce therapeutic effects [19]. Some drugs have an optimum concentration range within which maximum benefit is derived, and concentrations above or below this range can be toxic or produce no therapeutic benefit at all.

2. Conventional Dosage Forms

To minimize drug degradation and loss, to prevent harmful side-effects and to increase drug bioavailability and the fraction of the drug accumulated in the required zone, various drug delivery and drug targeting systems are currently under development Novel drug delivery system is a new approach to drug delivery. It helps the drug to act longer and more effectively.
This overcomes limitations of old methods of drug administration [20]. Drawbacks of conventional dosage forms. Conventional dosage forms possess following limitations [21].

- Poor patient compliance, increased chances of missing the dose of a drug with short half-life for which frequent administration is necessary.
- The unavoidable fluctuations of drug concentration may lead to under medication or over medication.
- A typical peak-valley plasma concentration time profile is obtained which make attainment of steady-state condition difficult.
- The fluctuations in drug levels may lead to precipitation of adverse effects especially of a drug with small therapeutic index whenever over medication occur.

3. Novel Drug Delivery Systems

In novel drug delivery technology; control of the distribution of drug is achieved by incorporating the drug in carrier system or in changing the structure of the drug at molecular level. Novel drug delivery systems possess following advantages [22].

- Enhancement of solubility.
- Increased bioavailability.
- Protection from toxicity.
- Enhancement of pharmacological activity.
- Enhancement of stability.
- Improved tissue macrophages distribution.
- Sustained delivery.
- Protection from physical and chemical degradation.

4. Herbal drugs

Herbal formulation means a dosage form consisting of one or more herbs or processed herb(s) in specified quantities to provide specific nutritional, cosmetic benefits, and/or other benefits meant for use to diagnose treat, mitigate diseases of human beings or animals and/or to alter the structure or physiology of human beings or animals.

Herbal preparations are obtained by subjecting whole plant, fragmented or cut plants, plants parts to treatments such as extraction, distillation, expression, fractionation, purification, concentration or fermentation. These include comminuted or powdered herbal substances, tinctures, extracts, essential oils, expressed juices and processed exudates [23-24].

4.1. Advantages of herbal drugs

Herbal drugs possess following advantages [25-27].

4.1.1. Low risk of side effects

Mostly herbal drugs are well tolerated by the patient, having fewer unintended consequences and fewer side effects than traditional medicine, and may be safer to use.

4.1.2. Effectiveness

Herbal drugs are more effective for long-standing health complaints that don't respond well to traditional medicine. One example is the herbs and alternative remedies used to treat arthritis. Vioxx, a well-known prescription drug used to treat arthritis, was recalled due to increased risk of cardiovascular complications. Herbal treatments for arthritis, on the other handle, have lesser side effects. Such treatments include dietary changes like adding simple herbs, eliminating vegetables from the nightshade family and reducing white sugar consumption.

4.1.3. Lower cost

Cost of herbal drugs is much less than prescription medications. Research, testing, and marketing add considerably to the cost of prescription medicines. Herbs tend to be inexpensive compared to drugs.
4.1.4. Widespread availability
Herbs are available without a prescription. Simple herbs, such as peppermint and chamomile, can be cultivated at home.

4.2. Limitations of herbal drugs
Herbal drugs possess following limitations [28-33].

4.2.1. Not suitable for many diseases
Modern medicine treats sudden and serious illnesses and accidents much more effectively than herbal or alternative treatments. An herbalist would not be able to treat serious trauma, such as a broken leg, nor would he be able to heal appendicitis or a heart attack as effectively as a conventional doctor using modern diagnostic tests, surgery, and drugs.

4.2.2. Lack of dosage instructions
Self-treatment with herbal drugs may consist of many risk factors. Moreover, with no proper direction of doses may lead to overdose.

4.2.3. Poison risk associated with wild herbs
Consumption of herbal drugs without correct identification of plant i.e., use of wrong part of plant may lead to poisoning.

4.2.4. Lack of regulation
Herbal products are not strictly regulated, consumers may buy inferior quality herbs. The quality of herbal products may vary among batches, brands or manufacturers. This can make it much more difficult to prescribe the proper dose of an herb. All herbal drugs are not safe, some may be poisonous or may cause allergic reactions.

4.2.5. Longer duration of treatment
Curing period is usually longer in comparison to conventional medication. Immense patience while undergoing herbal treatment is needed.

5. Novel Drug Delivery Systems (NDDS)
Herbal drugs are becoming more popular in the modern world for their application to cure variety of diseases with less toxic effects and better therapeutic effects. There is a great possibility for herbal drugs that many compounds will be destroyed in the highly acidic pH of the stomach. Other components might be metabolized by the liver before reaching the blood. As a result, the actual amount of the drug may not reach the blood. If the drug doesn’t reach the blood at a minimum level which is known as ‘minimum effective level’ then there will be no therapeutic effect [34].

5.1. NDDS for Delivery of Herbal Drugs
Drug delivery system used for administering the herbal medicine to the patient is traditional and out-of-date, resulting in reduced efficacy of the drug. Also, for long-time herbal medicines were not considered for development as novel formulations owing to lack of scientific justification and processing difficulties, such as standardization, extraction and identification of individual drug components in complex polyherbal systems [35]. Modern phytopharmaceutical research can solve the scientific needs such as determination of pharmacokinetics, mechanism of action, site of action, accurate dose required, etc [36].

5.2. Types of Novel Herbal Drug Delivery Systems
Various approaches in case of novel herbal drug delivery system includes different types of formulations such as liposomes, phytosomes, pharmacosomes, niosomes, nanoparticles, microspheres, transferosomes, ethosomes, transdermal drug delivery system and proniosomes, etc are discussed below (Fig. 1).
Figure 1 Novel drug delivery systems of herbal drugs [36]

5.2.1. Liposomes

Characteristics
Liposomes are spherical particles that encapsulate a fraction of the solvent, in which they freely diffuse or float into their interior. These are micro-particulate or colloidal carriers, usually 0.05-5.0µm in diameter which forms spontaneously when certain lipids are hydrated in aqueous media. They can have one, several or multiple concentric membranes [37]. Liposomes are constructed of polar lipids which are characterized by having a lipophilic and hydrophilic group on the same molecules.

The primary advantages of using liposomes include (i) the high biocompatibility, (ii) the easiness of preparation, (iii) the chemical versatility that allows the loading of hydrophilic, amphiphilic, and lipophilic compounds, and (iv) the simple modulation of their pharmacokinetic properties by varying the chemical composition of the player components (Fig. 2) [38].

Figure 2 Structure of liposomes [38]

Methods of preparation
All the methods of preparing the liposomes involve four basic stages:

- Drying down lipids from organic solvent.
- Dispersing the lipid in aqueous media.
- Purifying the resultant liposome.
- Analyzing the final product.

Advantages of liposome formulation
- Hydrophobic and hydrophilic drug can be delivered.
- Liposome herbal therapy acts as a carrier for small cytotoxic molecules and as vehicle for macromolecules as gene.
- Sustained and controlled release of formulation can be possible.
5.2.2. Phytosomes

Characteristics
Most of the bioactive constituents of phytomedicines are flavonoids, which are poorly bioavailable when taken orally. Water-soluble phytoconstituents molecules (mainly polyphenoles) can be converted into lipid-compatible molecular complexes, which are called phytosomes. Phytosomes are more bioavailable as compared to simple herbal extracts owing to their enhanced capacity to cross the lipid rich biomembranes and finally reaching the blood [39].

Method of preparation
Accurately weighed quantity of phosphatidylcholine and cholesterol were dissolved in 10 ml of chloroform in a round bottom flask (RBF) and sonicated for 10 min using bath sonicator. Organic solvent removal is done by Rotary evaporator (45-50°C). After complete removal of solvent, thin layer of phospholipids mixture was formed. This film was hydrated with methanolic extract of plant in rotary evaporator (37-40°C, 1 hr). After hydration, mixture of lipid and plant extract was sonicated for 20 min. in presence of ice bath for heat dissipation. Then prepared phytosomes were filled in amber colored bottle and stored in freezer (2-8 ºC) until used (Fig. 3) [40].

![Figure 3 Structure of phytosomes](image)

Advantages of Phytosomes
Phytosomes have the following advantages [41],

- Improve the absorption of lipid insoluble polar phytoconstituents, enhance the bioavailability.
- Appreciable drug entrapment which becomes very beneficial.
- Reduce the dose due to increased absorption.
- Phosphatidylcholine shows synergistic effect because it is a hepatoprotective also.
- Phytosomes are more stable because of the chemical bonding between the phytoconstituents and carrier i.e. phosphatidylcholine.
- Effective in cosmetics.

5.2.3. Nanoparticles

Characteristics
Nanoparticles are efficient delivery systems for the delivery of both hydrophilic and hydrophobic drugs. Nanoparticles are the submicron size particles having size range 10 to 1000 nm. The major goal behind designing nanoparticle as a delivery system are to control particle size, surface properties and release of pharmacologically active agents in order to achieve the site-specific action of the drug at the therapeutically optimal rate and dose regimen. In recent years, biodegradable polymeric nanoparticles have attracted considerable attention as potential drug delivery devices (Fig. 4) [42].

Method of preparation
- Solvent evaporation,
- Nanoprecipitation,
- Emulsification/solvent diffusion,
- Salting out,
- Dialysis,
- Supercritical fluid technology (SCF) [43].
Advantages of herbal nanoparticle delivery system

- Nanoparticulate system delivers the herbal formulation directly to the site of action.
- Encapsulating drugs within nanoparticles can improve the solubility and pharmacokinetics of drugs.
- Nanoparticles can also reach the choice of formulations, promote the drugs through the biological barriers and increase the bioavailability of drugs.
- It can take the drug directly to the site of action without destroying surrounding environment [44].

5.2.4. Niosomes

Niosomes are multilamellar vesicles formed from non-ionic surfactants of the alkyl or dialkyl polyglycerol ether class and cholesterol. Earlier studies, in association with L’Oreal have shown that, in general, niosomes have properties as potential drug carriers similar to liposomes [45].

Niosomes are different from liposomes in that they offer certain advantages over liposomes. Liposomes face problems such as they are expensive, their ingredients like phospholipids are chemically unstable because of their predisposition to oxidative degradation, they require special storage and handling and purity of natural phospholipids is variable. Niosomes do not have any of these problems [46].

5.2.5. Proniosomes

Proniosome gel system is step forward to niosome, which can be utilized for various applications in delivery of actives at desired site. Proniosomal gels are the formulations, which on in situ hydration with water from the skin are converted into niosomes. Proniosomes are water-soluble carrier particles that are coated with surfactant and can be hydrated to form a niosomal dispersion immediately before use on brief agitation in hot aqueous media [46].

Advantages of proniosomes

- More stable during storage and sterilization.
- Easy to transfer and distribution.

5.3. Transdermal Drug Delivery Systems

Transdermal drug delivery system has been an increased interest in the drug administration via the skin for both local therapeutic effects on diseased skin (topical delivery) as well as for systemic delivery of drugs. However, they did not have had such expected success with other drugs. But immense potential lies in transdermal drug as future smart drug delivery devices [47].

Transdermal delivery system provides the advantage of controlled drug delivery, enhanced bioavailability, reduction in side effects and easy application. Transdermal formulation of boswellic acid and curcumin has been developed for continuous drug administration [48].
5.3.1. Microspheres

Characteristics

Microspheres are discrete spherical particles ranging in average particle size from 1 to 50 microns. Microparticulate drug delivery systems are considered and accepted as a reliable one to deliver the drug to the target site with specificity, to maintain the desired concentration at the site of interest without untoward effects. Micro encapsulation is a useful method which prolongs the duration of drug effect significantly and improves patient compliance (Fig. 5) [49].

![Figure 5 Structure of microsphere](image)

Methods of preparation

- Spray Drying
- Solvent Evaporation
- Single emulsion technique
- Double emulsion technique
- Phase separation coacervation technique.
- Spray drying and spray congealing
- Solvent extraction
- Quassi emulsion solvent diffusion [50].

5.3.2. Ethosomes

Characteristics

Newer advancements in the patch technology have led to the development of ethosomal patch, which consists of drug in ethosomes. Ethosomal systems are made up of soya phosphatidylcholine, ethanol and water. They may form multilamellar vesicles and have a high entrapment capacity for molecules of various lipophilicities. The elastic vesicles and transferosomes have also been used as drug carriers for a range of small molecules, peptides, proteins and vaccines (Fig. 6) [51].

![Figure 6 Structure of ethosomes](image)

Method of preparation [52]

- Cold Method
- Hot Method
- Classic mechanical dispersion method
Advantages of ethosomal drug delivery

- Transdermal permeation of drug through skin can be enhanced.
- Large amounts of diverse groups of drugs can be delivered.
- The ethosomal drug is administered in semisolid form, resulting in improved patient compliance [53].

6. Analysis of NDSS systems of herbal drugs

NDSS systems containing either isolated phytoconstituents extracts or parts or whole drug are analyzed by routine quality control techniques. The quality control techniques includes high performance thin layer chromatography, high performance liquid chromatography, Uv-spectrophotometry, gas chromatography, etc [54-71]

7. Conclusion

By incorporating the herbal drugs in NDDS, we can deliver the proper amount of dosage to the target site. Thus it conclude that, NDDS for herbal drugs will be a revolutionary application in the conventional herbal formulations which will save the time of preparations and will increase the patient compliance too.

Compliance with ethical standards

Acknowledgments

We express our sincere thanks to Shri. Yogendraji Gode and Dr. Yogeshji Gode, IBSS’s Dr. Rajendra Gode Institute of Pharmacy, Amravati and Dr. Rajendra Gode College of Pharmacy, Amravati.

Disclosure of conflict of interest

Author declare that there is no conflict of interest.

References

[1] Charman WN, Chan HK, Finnin BC. Drug delivery: a key factor in realizing the full therapeutic potential of drugs, Drug Dev Res. 1999; 46: 316-327.
[2] Musthaba SM, et al. Status of novel drug delivery technology for phytotherapeutics. Expert Opin Drug Deliv. 2009; 6: 625-37.
[3] Badukale NA, et al. Phytochemistry, pharmacology and botanical aspects of Madhuca indica: A review. Journal of Pharmacognosy and Phytochemistry. 2021; 10(2): 1280-1286.
[4] Khadatkar SN, et al. Preparations and evaluation of microcapsules of capsacin. International Journal of Chemical Sciences. 2007; 5(5): 2333-2341.
[5] Sahare AY, et al. Hypericum perforatum: A Medicinal plant. Plant Archives. 2007; 7(2): 463-468.
[6] Manmode R, et al. Effect of preparation method on antioxidant activity of ayurvedic formulation kumaryasava. J Homeop Ayurv Med. 2012; 1: 114.
[7] Padgilwar S, et al. Traditional uses, phytochemistry and pharmacology of Oroxyllum Indicum: A Review. International Journal of Pharmaceutical and Phytopharmaceutical Research. 2014; 3(6): 483-486.
[8] Manwar J, et al. Isolation, biochemical and genetic characterizations of alcohol-producing yeasts from the flowers of Woodfordia fruticosa. J Young Pharm. 2013; 5(4): 191-194.
[9] Wadekar AB, et al. Morphology, phytochemistry and pharmacological aspects of Carica papaya, an review. GSC Biological and Pharmaceutical Sciences. 2020; 14(03): 234-248.
[10] Khadatkar SN, et al. In-vitro anthelmintic activity of root of Clitoria ternatea linn. 2008; 4(13): 148-150.
[11] Sahare AY, et al. Antimicrobial activity of Pseudarthria viscida roots. Asian Journal of Microbiology Biotechnology & Environmental Sciences. 2008; 10(1): 135-136.
[12] Gudalwar BR, et al. Allium sativum, a potential phytopharmacological source of natural medicine for better health. GSC Advanced Research and Reviews. 2021; 06(03): 220–232.
[13] Malode GP, et al. Phytochemistry, pharmacology and botanical aspects of Murraya Koenigii in the search for molecules with bioactive potential - A review. GSC Advanced Research and Reviews. 2021; 06(03): 143–155.

[14] Nikhare AM, et al. Morphological, Phytochemical and pharmacological aspects of Syzigium Cumini. International Journal of Medical, Pharmaceutical and Biological Sciences. 2021; 1(1): 1-11.

[15] Bijewar AH, et al. Overture in development, properties and clinical aspects of biosurfactants: An review. International Journal of Medical, Pharmaceutical and Biological Sciences. 2021; 1(1): 1-12.

[16] Parbat AY, et al. Ethnopharmacological review of traditional medicinal plants as immunomodulator. World Journal of Pharmacy and Health Sciences. 2021; 06(02): 043-055.

[17] Dongare PN, et al. An Overview on herbal cosmetics and cosmeceuticals. Int J Pharm Sci Rev Res. 2021; 68(1): 75-78.

[18] Biju SS, Talegaonkar S, Khar RK. Vesicular system: an overview. Indian J Pharm Sci. 2006; 68(2): 141-153.

[19] Sharma A, Sharma US. Liposomes in drug delivery: progress and limitations. Int J Pharm. 1997; 154: 123-40.

[20] Saraf AS. Applications of novel drug delivery system for herbal formulations. Fitoterapia. 2010; 81: 680-9.

[21] Sharma G, Anabousi S, Ehrhardt C, Ravi Kumar MN. Liposomes as targeted drug delivery systems in the treatment of breast cancer. J Drug Target. 2006; 14: 301-10.

[22] Ajazuddin, Saraf S. Applications of novel drug delivery system for herbal formulations. Fitoterapia. Elsevier B.V. 2010; 81(7): 680–9.

[23] Chaturvedi M, Kumar M, Sinhal A, Saifi A. Recent development in novel drug delivery systems of herbal drugs. Int J Gr Pharm. 2011; 5(2): 87-94.

[24] Semalty A, Semalty M, Rawat MSM. The Phyto-phospholipid complexes- phytosomes: a potential therapeutic approach for herbal hepatoprotective drug delivery. Pog rev. 2007; 1(2): 369-74.

[25] Goyal A, Kumar S, Nagpal M, Singh I, Arora S. Potential of novel drug delivery systems for herbal drugs. Ind J Pharm Educ Res. 2011; 45(3): 225-35.

[26] Mohanraj VJ, Chen Y. Nanoparticles: a review. Trop J Pharm Res. 2006; 5(1): 561-73.

[27] Saraf AS. Applications of novel drug delivery system for herbal formulations. Fitoterapia. 2010; 81: 680-9.

[28] Nagavarma BVN, Yadav HKS, Ayaz A, Vasudha LS, Shivakumar HG. Different techniques for preparation of polymeric nanoparticles- A review. Asian J Pharm Clin Res. 2012; 5(3): 16-23.

[29] Tangri P, Khurana S. Niosomes: Formulation and evaluation. Int J Biopharm. 2011; 2(2): 47-53.

[30] Gupta S, Singh RP, Lokwani P, Yadav S, Gupta SK. Vesicular system as targeted drug delivery system: an overview. Int J Pharm Tech. 2011; 3(2): 987-1021.

[31] Shukla ND, Tiwari M. Proniosomal drug delivery systems - Clinical applications. Int J Res Pharm Biomed Sci. 2011; 2(3): 880-7.

[32] Goyal C, Ahuja M, Sharma SK. Preparation and evaluation of anti-inflammatory activity of gugulipid-loaded proniosomal gel. Acta Pol Pharm Drug Res. 2011; 68(1): 147-50.

[33] Rav GS, Dubey A, Hebbar, S. Development of maltodextrin based proniosomes derived niosomes of Ofloxacin. Int. J. Pharm. Sci. Res. 2019; 10(3): 1485-1490.

[34] Madni A, et al. Enhancement of dissolution and skin permeability of pentazocine by proniosomes and niosomal gel. AAPS PharmSciTech. 2018; 19(4): 1544-1553.

[35] Ahmad MZ, et al. Technology overview and drug delivery application of proniosome. Pharm. Dev. Technol. 2017; 22(3): 302–311.

[36] Prasad NS, et al. Augmentation of dissolution profile of poorly soluble Olmesartan medoximil formulating into proniosomes. European JBPS. 2016; 3(2): 122-128.

[37] Abdallah MH, Sabry SA, Hasan AA. Enhancing transdermal delivery of glimepiride via entrapment in proniosomal gel. J Young Pharm. 2016; 8(4): 335-340.

[38] Cheriyan P, et al. Formulation and characterization of maltodextrin based proniosomes of cephalosporins. Pharm. Sci. 2015; 3(1): 62-74.
[39] Asijia R, et al. Development of proniosomes gel as a drug carrier for transdermal delivery of acyclovir. J Drug Deliv Ther. 2014; 2(18): 41-51.

[40] Soujanya CP, Ravi P. Development and in vivo evaluation of lovastatin loaded transdermal proniosomal gel by design of experiment. Int. J. Pharm. Sci. Drug Res. 2018; 10(4): 252-259.

[41] Lather V, Sharma D, Pandita D. Proniosomal gel-mediated transdermal delivery of bromocriptine: in vitro and ex vivo evaluation. J Exp Nanosci. 2016; 11(13): 1044-1057.

[42] Yuksel N, et al. In situ niosome forming maltodextrin proniosomes of candesartan cilexetil: In vitro and in vivo evaluations. Int. J. Biol. Macromol. 2016; 82: 453-63.

[43] Jukanti R, et al. Provesicular drug delivery systems: An overview and appraisal. Arch. Appl. Sci. Res. 2010; 2(4): 135-146.

[44] Ramkanth S, et al. Development, characterization & in vivo evaluation of proniosomal based transdermal delivery system of Atenolol. Future J. Pharm. Sci. 2018; 4(1): 80-87.

[45] Benipal G. Design, development and evaluation of proniosomal gel of an antifungal drug- Ketoconazole. Int J Pharm Sci Rev Res. 2018; 31(2): 265-277.

[46] Vyas SP, Khar RK. Niosomes targeted and controlled drug delivery. CBS Publishers and Distributors. 249-279.

[47] Seetha Devi, et al. Formulation and evaluation of candesartan cilexetil transdermal proniosomal gel. J. Drug Deliv. Ther. 2014; 4(2): 90-98.

[48] Chinga NL, Gupta M. Preparation and characterization of metformin proniosomal gel for treatment of diabetes mellitus. Asian J. Pharm. Sci. 2020; 15: 13-25.

[49] AlsaarAg, et al. Proniosomes as a drug carrier for transdermal delivery of ketorolac. Eur J Pharm and Biopharm. 2004; 105: 1-6.

[50] Rajkumar J, et al. Recent update on proniosomal gel as topical drug delivery system. Asian J Pharm Clin Res. 2019; 12(1): 54-61.

[51] Aswathi et al. A review on proniosomes- controlled drug delivery system. Indo Am. J. Pharm. Sci. 2018; 5(8): 7584-7589.

[52] Upadhye et al. Proniosomes: A novel vesicular drug delivery system. Am. J. PharmTech Res. 2020; 10(2): 260-273.

[53] Nimbalwar MG, Upadhye K, Dixit G. Fabrication and evaluation of ritonavir Proniosomal transdermal gel as a vesicular drug delivery system. Pharmacophore. 2016; 7(2): 82-95.

[54] Sabbadinde AF, et al. Novel RP-HPLC method for simultaneous analysis of chlorthalidone and telmisartan from combined dosage form. Jippr.Human. 2020; 20(1): 491-502.

[55] Panchale WA, et al. RP-HPLC method for simultaneous determination of escitalopram oxalate and flupentixolHCl in tablet dosage form. GSC Biological and Pharmaceutical Sciences. 2021; 14(01): 169-174.

[56] Nimbokar SW, et al. Development and validation of RP-HPLC method for determination of zonisamide from tablet formulation. World Journal of Pharmaceutical and Medical Research. 2021; 7(2): 196-200.

[57] Panchale WA, et al. RP-HPLC method for simultaneous determination of metformin hydrochloride and linagliptine in pharmaceutical dosage form. World Journal of Pharmaceutical and Medical Research. 2021; 7(5): 234-238.

[58] Manwar JV, et al. Development of newer RP-HPLC method for simultaneous estimation of cefixime and linezolide in bulk drugs and combined dosage form. International Journal of Pharmacy and Life Sciences. 2021; 12(1): 26-31.

[59] Panchale WA, Gulhane CA, Manwar JV, Bakal RL. Simultaneous estimation of salbutamol sulphate and ambroxol HCl from their combined dosage form by UV-Vis spectroscopy using simultaneous equation method. GSC Biological and Pharmaceutical Sciences. 2020; 13(03): 127-134.

[60] Bakal RL, et al. Spectrophotometric estimation of amitriptyline HCl and chlordiazepoxide in tablet dosage form. International Journal of Chemical Sciences. 2007; 5(1): 360-364.

[61] Panchale WA, Bakal RL. First-order derivative spectrophotometric estimation of gemifloxacin mesylate and ambroxol HCl in tablet dosage form. GSC Biological and Pharmaceutical Sciences. 2021; 14(2): 029-036.
[62] Gulhane CA, et al. Liquid chromatographic method for simultaneous estimation of thiocolchicoside and etoricoxib from tablet formulation. Asian Journal of Pharmaceutical Analysis. 2021; 11(2): 118-122.

[63] Panchale WA, et al. Chromatographic analysis of famotidine, paracetamol and ibuprofen from tablet formulation. Research Journal of Pharmacy and Technology. 2019; 12: 231-263.

[64] Manwar JV, et al. Application of simultaneous equation method for the determination of azithromycin and cefixime trihydrate in tablet formulation. Research Journal of Pharmacy and Technology. 2017; 10(1): 108-112.

[65] Manwar JV, et al. Response surface based optimization of system variables for liquid chromatographic analysis of candesartan cilexetil. Journal of Taibah University for Science. 2017; 11: 159–172.

[66] Manwar J, Mahadik K, Paradkar A, et al. Gas chromatography method for the determination of non-ethanol volatile compounds in herbal formulation. International Journal of Analytical and Bioanalytical Chemistry. 2013; 3(1): 12-17.

[67] Panchale WA, et al. Concurrent analysis of ambroxol HCl and salbutamol sulphate from tablet formulation by RP-HPLC. GSC Biological and Pharmaceutical Sciences. 2020; 13(03): 197-202.

[68] Manwar JV, et al. Experimental design approach for chromatographic determination of ketorolac tromethamine from bulk drug and tablet formulation. Global Journal of Pharmacy & Pharmaceutical Sciences. 2017; 3(2): 38-47.

[69] Manmode RS, et al. Stability indicating HPLC method for simultaneous determination of methocarbamol and nimesulide from tablet matrix. Der Chemica Sinica.2011; 2(4): 81-85.

[70] Bagade SB, et al. Simultaneous high performance thin layer chromatographic estimation of methocarbamol and nimesulide in combined dose tablet. Journal of Pharmaceutical Research. 2006; 5(4): 137-140.

[71] Gulhane CA, et al. UV- Visible Spectrophotometric estimation of azithromycin and cefixime from tablet formulation by area under curve method. World Journal of Pharmaceutical Sciences. 2021; 9(6): 163-168.