International Journal of Pharmaceutical research and Applications
Volume 8, Issue 6, Nov.-Dec. 2023, pp: 1814-1822 www.ijprajournal.com ISSN: 2456-4494

Transdermal Patch Overview: Revolutionizing Drug Delivery

Devadatta Salve[1*], Swati Talele[2], Laxmikant Bore[3]
Department of Pharmaceutical Sciences, Sandip Institute of Pharmaceutical Science's, Affiliated Savitribai Phule Pune University Mahiravni, Nashik—422213, MS, India
Department of Pharmaceutical Sciences, Sandip Institute of Pharmaceutical Sciences, Affiliated Savitribai Phule Pune University Mahiravni, Nashik—422213, MS, India
Department of Pharmacology, Sandip Institute of Pharmaceutical Sciences, Affiliated Savitribai Phule Pune University Mahiravni, Nashik—422213, MS, India

Date of Submission: 04-12-2023 Date of Acceptance: 17-12-2023

Abstract
The transdermal patch has emerged as a breakthrough technology in the field of drug delivery, offering a non-invasive and convenient alternative to traditional methods such as oral administration or injections. This paper provides an overview of transdermal patches, their composition, and the principles behind their successful drug delivery mechanism.
The overview begins by highlighting the advantages of transdermal patches, including their ability to provide controlled release of medications, improved patient compliance, and reduced systemic side effects. The composition of transdermal patches is explored, focusing on the key components such as the drug reservoir, adhesive layer, and backing material. The various types of drugs that can be administered through transdermal patches are discussed, ranging from pain relief medications and hormone therapies to nicotine replacement products and motion sickness treatments.
Furthermore, the overview delves into the mechanisms of drug delivery through the skin barrier, including the factors that influence permeation, such as molecular weight, lipophilicity, and skin condition. The importance of enhancers, which aid in enhancing drug permeation, is also examined. The role of formulation technologies, including reservoir and matrix systems, in achieving desired drug release profiles is explained.
The paper also explores the challenges associated with transdermal patch development, such as maintaining drug stability, achieving consistent drug release, and addressing individual variations in skin properties. Strategies to overcome these challenges, such as the use of innovative adhesive systems and the integration of micro- and nano-technologies, are highlighted.
In conclusion, the transdermal patch represents a promising and evolving approach to drug delivery, with the potential to revolutionize the pharmaceutical industry. This overview provides valuable insights into the composition, mechanisms, and challenges of transdermal patches, paving the way for further research and development in this exciting field.
Keywords: Neuropathic pain, Multilayer drug-in-adhesive, Matrix-distribution system, Vapour Patch.

I. Introduction
Althoughthe oral route is the most widely used method of drug delivery, it has certain drawbacks, including the first pass metabolism, drug degradation, etc. owing to enzymes, pH, etc. in the gastrointestinal tract. Chien and Banker created a unique medication delivery technology in 1992 and 1990, respectively, to solve these issues. It was a transdermal delivery system or transdermal patches. In this approach, therapeutically effective medication doses are delivered to the skin when medicated adhesive patches are applied to the skin. They come in different sizes and include multiple ingredients. They penetrate skin barriers to transfer active compounds into systemic circulation once applied to intact skin. A transdermal patch that is applied to the skin and left there for a long time, allowing a high dose of medication to diffuse into the bloodstream.

The fundamental goal of a transdermal drug delivery system is to deliver medications into the bloodstream through the skin at a predefined pace with little patient-to-patient variability. Additionally, it is well acknowledged that

International Journal of Pharmaceutical research and Applications
Volume 8, Issue 6, Nov.-Dec. 2023, pp: 1814-1822 www.ijprajournal.com ISSN: 2456-4494

transdermal patches promote patient compliance because they are easy to use, handy, painless, and allow multi-day dosage.

It is mostly used to treat neuropathic pain (pain in the nerves), particularly in sensitive-to-touch areas. In addition to being effective for treating Post Herpetic Neuralgia, transdermal patches have also been reported to be effective for treating other neuropathic pain conditions. [1,2].

Topical drug administration affects tissues near the application site, while systemic drug delivery affects tissues after the drug has circulated throughout the body (systemic delivery). The barrier qualities of the skin present a substantial problem despite the fact that medicine delivery through the skin has several benefits. It will be able to develop methods for enhancing drug delivery by understanding the mechanisms by which chemicals cross the skin. [3].

Thermodynamic activity of the drug in the formulation, interaction of the drug and formulation with the skin, and differences in skin with age, race, anatomical location, and disease are just a few of the numerous factors that can affect how quickly medications are delivered through the skin.

Getting medicine intobloodstream through the skin is viewed as a better option than taking it by mouth or orally. Patients frequently fail to take their medication, and even the most obedient patients become tired of swallowing pills, especially if they must take many each day. In addition, skipping the gastrointestinal (GI) system would eliminate GI discomfort and partial first pass activation by the liver. Furthermore, consistent drug absorption over hours or days is usually preferable to the blood level spikes and troughs caused by oral dosing forms. These benefits are provided via transdermal products [3].

Transdermal medication delivery provides some advantages over conventional methods of drug administration, which leads to higher patient compliance. Because of its non-invasive nature, ease of application and removal, predefined rate of drug permeation, enhanced bioavailability of medication, and lower hepatic metabolism, this method is best suited for systemic drug delivery over lengthy time periods of 24 hours.

Drugs can enter through skin in three ways-

a) Through the hair follicle.
b) Through the sebaceous glands.
c) Through sweat ducts.

Transdermal drug delivery systems are used in a variety of skin conditions, as well as treating neurological conditions such as angina, pain, smoking cessation, and Parkinson's disease. Transdermal drug delivery systems are used in a variety of skin disorders, including the treatment of angina pectoris, pain, smoking cessation, and neurological disorders such as Parkinson's disease [1,2].

Drugs are delivered in controlled amounts through the skin using transdermal, adhesive, or dermal patches over time. The rate at which fluids from reservoirs inside dermal patches move through the skin and into the bloodstream is controlled by a particular membrane. Some medications need to be mixed with substances like alcohol to boost their capacity to enter the skin when used as skin patches. Among the medications applied as skin patches is scopolamine (for motion sickness),nicotine (to help quit smoking), estrogen (to prevent menopause and postmenopausal osteoporosis), and nitroglycerin (for angina), lidocaine to relieve shingles pain, and many other drugs [4].

Application site has been shown to affect the penetration flux into human skin (Pastore et al., 2015). Many body sections (such as the trunk and upper arm) seem to have comparable fluxes, enabling interchangeable patch implantation to produce comparable plasma concentrations over time. wearable time. recommended (Pastore et al., 2015). Testosterone, nicotine, norelgestromin, estradiol and clonidine all show similar plasma concentrations, with similar absorption at different skin sites. However, studies have shown that rivastigmine shows higher plasma exposure after application to the upper back, chest, or upper arms than to the thighs or abdomen. Details of these studies are available, but it is important to follow the advice of trained healthcare professionals to apply them to ensure efficacy. thanks to the right dose and the right treatment.

1. Neuropathic pain

Neuropathic pain (NP) is a pathological process in the peripheral or central nervous system. It is defined by the International Association for the Study of Pain (IASP) as pain caused by a lesion or disease of the somatosensory nervous system [5]. Although many NP disorders are caused by damage to the peripheral nervous system, their chronicity appears to be based on maladaptive processes within the CNS. Neuronal hyperexcitability and central sensitization alter pain processing, leading to spontaneous pain and pathologically enhanced responses to noxious and non-noxious stimuli [6]. Resulting symptoms include allodynia (pain

International Journal of Pharmaceutical research and Applications
Volume 8, Issue 6, Nov.-Dec. 2023, pp: 1814-1822 www.ijprajournal.com ISSN: 2456-4494

resulting from stimuli that normally do not cause pain) and hyperalgesia. Patients experience bouts of burning, shooting, electrical sensations, and painful painless numbness [7]. Examples of NPs include postherpetic neuralgia (PHN), diabetic peripheral neuropathy (DPN), carpal tunnel syndrome, complex regional pain syndrome, and post-traumatic/postoperative pain [8]. Pharmacological treatment options for NP include antidepressants, anticonvulsants, local anesthetics, and opioids [9,10].

Clinical practice guidelines for NP have been published by many organizations, including the European Federation of Neurological Societies (EFNS) [11], the National-Institutes-of-Health (NICE) [12], and the International Research Society [13]. Pain and the Canadian-Pain-Society (CPS) [14].

PHN is a painful neuropathy characterized by persistent allodynia or hyperalgesia in areas of previous herpes zoster [15]. It typically occurs on one side ofskin, the most common sites being the ocular region of the thoracic and trigeminal nerves [16]. It is more common in the elderly and immunocompromised patients, and has been reported to increase health resource utilization and adversely affect quality of life (QoL) [15,17]. There are various treatment guidelines, and the majority of them suggest drugs such tricyclic antidepressants, gabapentin, and lidocaine patch, and opioids to treat pain associated with postherpetic neuralgia. [11, 13, 18].

Clinical trials shown that transdermal patches for treatment of PHN are effective and well-tolerated, with minimal risk of systemic side effects and drug-drug interactions [19-21]. In the United States, prescription lidocaine patches are FDA-approved only for the relief of PHN-related pain. They are recommended as 1st-line treatment for PHN by the guidelines of the American Academy of Neurology (withdrawn in 2018) [18], the European Federation Neurological Societies [11], and the Canadian-Pain-Society [14].

2. Benefits

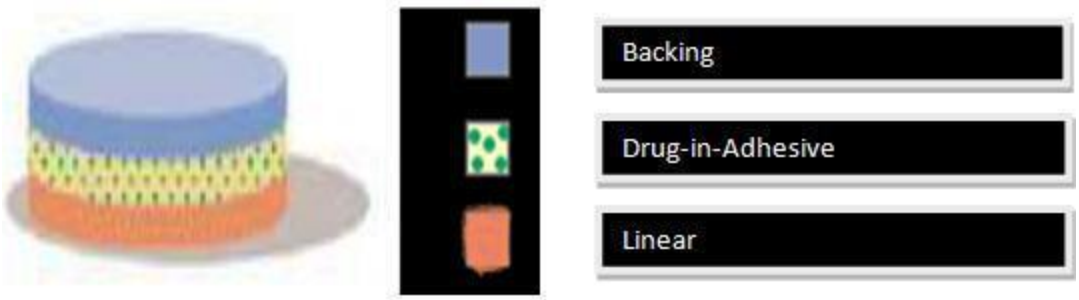
The route for transdermal administration is an interesting option because it is convenient and safe. Beneficial properties of drugs administered through the skin to achieve systemic effects are:

a) avoids firstpass metabolism of the drug;
b) Gastrointestinal intolerance is avoided.
c) Self-medication is possible.
d) The period of action is long and predictable.
e) Minimize unwanted side effects.
f) plasma drug concentrations are maintained;
g) Reduced dosing frequency and improved patient compliance.
h) Avoidance of problems increases the therapeutic value of many drugs associated with drug-like absorption, gastrointestinal irritation, and degradation by hepatic first-pass metabolism[22, 23].
i) Providing narrow use of drugs with short biological half-lives treatment window.
j) improved physiological and pharmacological responses.
k) Avoid fluctuating drug levels;
l) Between and within patient variations.
m) Maintaining plasma concentrations of active drug. n) Termination of treatment is possible at any time.
n) Improves patient compliance by eliminating multiple dosing profiles 24].

3. Patch design and type

- **Single layer drug-in adhesive**

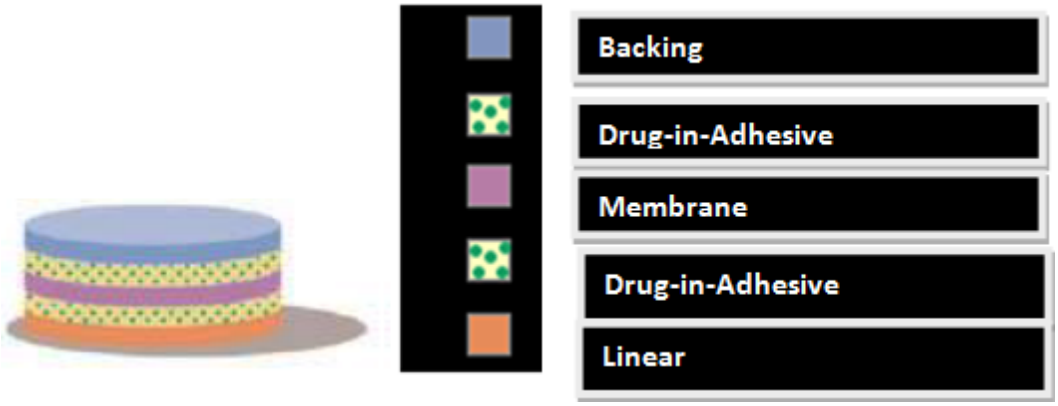
This system also has a medication in the sticky layer. In this kind of patch, adhesive layer aids in the medication release as well as adhering the various layer's together with the overall system on the skin. A temporary liner and backing encircle the adhesive layer. The benefit is that the medication is immediately mixed with the skin-adhesive glue before being administered to the epidermis.



International Journal of Pharmaceutical research and Applications
Volume 8, Issue 6, Nov.-Dec. 2023, pp: 1814-1822 www.ijprajournal.com ISSN: 2456-4494

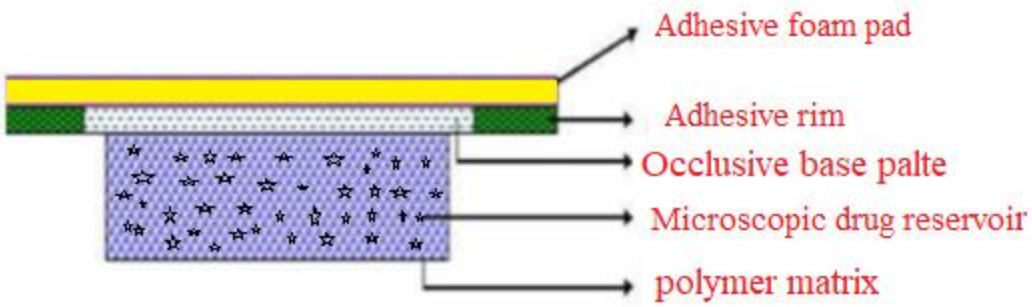
➢ **Multilayer drug-in-adhesive**

Monolayer systems are similar to multilayer medical adhesive patches. But multilayer systems are different because they often add an additional sticky layer that is separated from it by a membrane (but not in all cases). 1 of the layers is for quick medication release, and the other is for reservoir-controlled drug release. This patch also features a permanent backing and a transient liner layer. The permeability of the membrane and the drug molecules' capacity to diffuse determine the drug release from it.



➢ **TDDS with Micro reservoir Control:**

This drug delivery method combines a matrix dispersion device and a reservoir. The medication is initially suspended in an aqueous solution of a water-soluble polymer to create a drug reservoir. This solution is then uniformly dispersed in a lipophilic polymer to form thousands of unattainable microscopic drug-reservoir globules. Thermodynamically unstable dispersions are rapidly stabilized by instantaneous in situ crosslinking of the polymers. Therefore, the therapeutic system of the transdermal system is configured as a medical disc that is centrally located and surrounded by an adhesive rim (Patani and Chien, 1999).

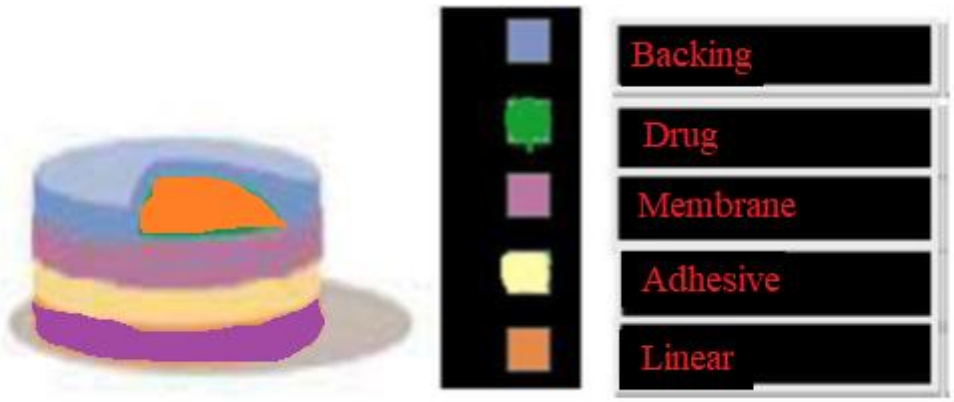


➢ **Matrix system:**

1) Adhesive system:

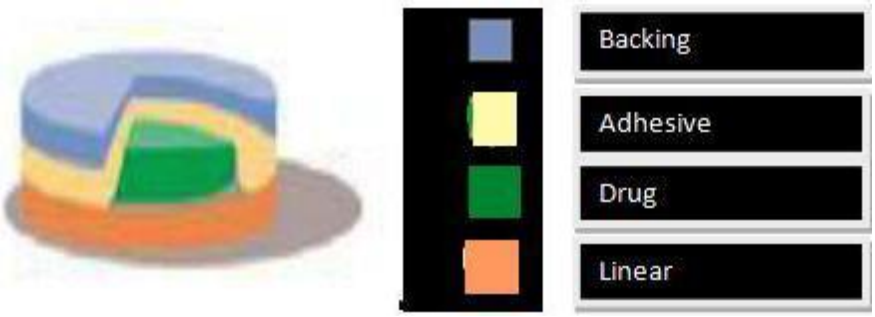
This type of drug tank is created by distributing the drug in an adhesive polymer and the drug-containing adhesive polymer in an impermeable layer using solvent casting or melting the backing layer. A directly adhering polymer layer is applied to the reservoir for protection (Brown and Jones, 2000).

International Journal of Pharmaceutical research and Applications
Volume 8, Issue 6, Nov.-Dec. 2023, pp: 1814-1822 www.ijprajournal.com ISSN: 2456-4494



2) Matrix-distribution system

In this type, the drug is uniformly dispersed in hydrophilic or lipophilic polymer matrix. This drug-laden polymer disc is fixed to an occlusive baseplate within a compartment made of a drug-impermeable backing sheet. Instead of applying the adhesive to the surface of the drug reservoir, it is spread around to form adhesive boundary (Brown and Jones, 2000; Tsai et al., 1998).



➢ **Vapour Patch**

In vapor patches, the adhesive film not only bonds different films together, but also plays the role of releasing vapors. Vapor patches release crucial oils for up to six hours and are primarily used for decongestion. Other vapor patches on the market can improve sleep quality or help you quit smoking.

4. Drug delivery by topical and transdermal patch system

The outermost layer of epidermis, the stratum corneum, provides the skin's primary barrier function. The stratum corneum composed of multiple layers of corneocytes packed in a multilayered lipid matrix [25,26,27]. Skin penetration of drugs is determined by the product's solubility and diffusivity in the stratum corneum [25, 26]. Drugs that can diffuse through the skin are generally lipophilic and of low molecular weight (<500 Daltons) [25,28]. The process of drug crossing this barrier begins with release ofdrug from the adhesive layer of the patch. Diffusion into the stratum corneum occurs passively or with the aid of penetration enhancers. After passing through the stratum corneum, the drug disperses into a more aqueous environment in deeper layers of dermis and is absorbed into the cutaneous circulation, thereby entering the systemic circulation. It is intended to deliver drugsto body and be absorbed into the circulation and made systemically available [26]. Penetration enhancers that interact with the intracellular lipid matrix of stratum corneum, such as ethanol, oleic acid, propylene glycol, and triacetin, are commonly used in transdermal patch systems to enhance drug penetration [29].In contrast, topical application of anesthetic patches in treatment of local pain results in mean peak blood concentrations that are about 1/10th those required to treat cardiac arrhythmias and 1/38th those that cause toxicity. [30, 8]. Therefore, the risk of adverse event's associated with systemic exposure when using topical patch systems is usually limited.

5. Patch attributes

International Journal of Pharmaceutical research and Applications
Volume 8, Issue 6, Nov.-Dec. 2023, pp: 1814-1822 www.ijprajournal.com ISSN: 2456-4494

1. ADHESION – SAFETY, EFFECTIVENESS AND QUALITY CHARACTERISTICS OF PATCH SYSTEMS

The adhesive should be non-irritating and non-irritating to the skin. The three basic attributes associated with patch adhesion are tack, shear, and peel. [32]

Tack is the capacity of a patch to swiftly and lightly cling to all skin type upon initial contact [32]. Consequently, gypsum-based adhesives are referred to as "pressure sensitive adhesives" by their manufacturers (PSAs). I'm predicting it. Application times for prescription pain management patch systems range from 30 min to 7 day's [33, 34]. Patch system cost, effectiveness, and safety may be impacted by adhesion problems. Patch lift, a phenomenon brought on by poor adhesion, results in insufficient drug administration and dosage. [32].

2. Delivery of medicines

Patch thickness may have an impact on medication delivery. Only a small portion of the medicine diffuses to the skin when there is a thick (DIA) layer or reservoir layer. minimise the possibility of it getting stuck on clothing, bedding, or a chair or being scratched, peeled off, or caught. These ($10_{cm} \times 14_{cm}$) patch systems have demonstrated to be bioequivalent in terms of delivering the same quantity of medication through skin. While the 5% hydrogel patch's estimated bioavailability is only 3–2%, the 1.8% patch's medication bioavailability is roughly 48%. [34].

3. Drug Remains in Patch Systems

The quantity of drug residue left on patch after use is another crucial aspect of patch systems. Typically, transdermal delivery systems are made to hold more medication thanpatch actually disperses. After the intended time of use, commercially available patch systems leave behind drug residues that range from 10% to 95% [35]. Increased patient dosages and/or protracted pharmacological effects may be the result of failing to remove patch system at conclusion of the authorized use period [35]. 32 unintentional patch exposures to fentanyl over a 15-year period were reported in 2012. Most of the time, young toddlers under 2 were involved [36].

6. Factors Affecting Patches

pH value

The pH of skin is normally acidic, ranging from pH 4 to pH 6 [37-38], while the internal environment is approximately neutral pH, ranging from 7-9.

Skin pH is a product of the water-soluble components of stratum corneum, secreted sweat and sebum, and eliminates carbon dioxide. [39].

Temperature

The skin becomes more permeable when warm. Heat has been found to increase the kinetic energy of proteins, lipids and carbohydrates in cell membranes and drug molecules. This increases drug migration into the dermis but decreases local drug delivery. Studies have shown a change in temperature of approximately 5°C is required to change permeability of the cell membrane. [40].

molecular weigh

It can affect the diffusion coefficient of the drug in question. Although the preferred molecular weight for passive diffusion drug transdermal drug delivery system is less than 500 Daltons, the permeation rate can be increased by using various penetration enhancers. [41].

partition coefficient

Log P, or partition coefficient, determines the distribution of a drug in vivo and is essential for exerting biological activity. When applied topically, hydrophilic medications have poor penetration through the stratum corneum's lipid matrix and poor absorption. Tissue levels may decrease as skin blood flow rapidly removes absorbed drug [42].

hydration

Permeability of most drugs is increased by hydration of the stratum corneum. It does this by opening the dense structure of the stratum corneum, thereby improving the bioavailability of the drug [43].

The flux across skin depends on skin hydration, distribution and transport across the stratum corneum, and concentration gradients across the skin. [44].

Age

The pH of skin surface changes with age. Unbound water molecules that are not bound to proteins found in the skin increase with age and may slow transdermal penetration, especially of hydrophilic drugs. The content of important lipids, especially ceramides, also decreases with age [45].

Gender

The study found no statistical difference in stratum corneum thickness or number of cell layers. Males

International Journal of Pharmaceutical research and Applications
Volume 8, Issue 6, Nov.-Dec. 2023, pp: 1814-1822 www.ijprajournal.com ISSN: 2456-4494

are known to have thicker cell epidermis than females. [46].

Body part

According to the studies conducted, the stratum corneum has the lowest number of cells in the pubic area and the highest number of cells in the heels [47].

Sun exposure

The stratum corneum is thicker in sun-exposed areas than in the thinner stratum corneum in sunburned areas [48].

skin condition

In neurodermatitis, the ability of stratum corneum to bind water is reduced, resulting in dry and inelastic skin in AD patients. Changes in the composition of intercellular lipids due to elevated cholesterol levels and decreased ceramide levels contribute significantly to impaired barrier function. Additionally, pH level of skin is higher than it is in healthy skin.[49].

References

[1]. Klein-Marcuschamer D, Ajikumar PK, Stephanopoulos G (2007) Engineering microbial cell factories for biosynthesis of isoprenoid molecules: beyond Iycopene. Trends Biotechnol25, 417-424.
[2]. Clomburg JM, Gonzalez R (2010) Biofuel production in Escherichia coli: the role of metabolic engineering and synthetic biology. Appl Microbiol Biotechnol86, 419-434.
[3]. Hatti-Kaul R, Tornvall D, Gustafsson L, Borjesson P (2007) Industrial biotechnology for the production of bio-based chemicals - a cradle-to-grave perspective. Trends Biotechnol25, 119-124.
[4]. Singh JS, Abhilash PC, Singh HB, Singh RP, Singh DP (2011) Genetically engineered bacteria: An
[5]. emerging tool for environmental remediation and future research perspectives. Gene 480, 1-9.
[6]. Covert MW, Schilling CH, Famili I, Edwards JS, Goryanin II, et al. (2001) Metabolic modeling of microbial strains in silico. Trends Biochem Sci 26, 179-186.
[7]. Menten L, Michaelis MI (1913) Die Kinetik der Invertinwirkung. Biochem Z 49,333-369.
[8]. Monod J (1949) The growth of bacterial cultures. Annu Rev MicrobioI3,371-394.
[9]. Bailey JE (1998) Mathematical modeling and analysis in biochemical engineering: Past accomplishments and future opportunities. Biotechnol Prog 14, 8-20.
[10]. Ho Y, Kiparissides A, Pistikopoulos EN, Mantalaris A (2012) A computational approach for understanding and improving GS-NSO antibody production under hyperosmotic conditions. J BiosciBioeng 113, 88-98.
[11]. Kiparissides A, Koutinas M, Kontoravdi C, Mantalaris A, Pistikopoulos EN (2011) "Closing the loop" in biological systems modeling - from the in silico to the in vitro. Automatica 47, 1147- 1155.
[12]. Kiparissides A, Kucherenko S, Mantalaris A, Pistikopoulos EN (2009) Global sensitivity analysis challenges in biological systems modeling. Ind Eng Chem Res 48, 7168-7180.
[13]. Kontoravdi C (2006) Development of a combined mathematical and experimental framework for modelling mammalian cell cultures. Ph.D. Thesis, Department of Chemical Engineering and Chemical Technology, Imperial College, London.
[14]. Kontoravdi C, Pistikopoulos EN, Mantalaris A (2010) Systematic development of predictive mathematical models for animal cell cultures. Comput Chem Eng 34, 1192-1198.
[15]. Saltelli A, Chan K, Scott EM (2000) Sensitivity analysis. Wiley Press.
[16]. Kyparissidis A (2012) Development of a combined mathematical and experimental framework for the control and optimisation of mammalian cell culture systems. Ph.D. Thesis, Department of Chemical Engineering and Chemical Technology, Imperial College, London.
[17]. Alper H, Jin YS, Moxley JF, Stephanopoulos G (2005) IdentifYing gene targets for the metabolic engineering oflycopene biosynthesis in Escherichia coli. Metab Eng 7, 155-164.
[18]. De Jong H (2002) Modeling and simulation of genetic regulatory systems: A literature review. J ComputBioI 9, 67-103.
[19]. Pecou E (2005) Splitting the dynamics of large biochemical interaction networks. J TheorBioI 232, 375-384.
[20]. Hasty J, McMillen D, Isaacs F, Collins JJ (2001) Computational studies of gene regulatory networks: in numero molecular biology. Nat Rev 2 ,268-279.

[21]. Masojidek J, Torzillo G. Mass cultivation of fresh water microalgae. Encyclopedia of Ecology 2008;2226–35.
[22]. Chisti Y. Biodiesel from microalgae. Biotechnology Advances 2007;25:294– 306
[23]. Hu Q, Guterman H, Richmond A. A flat inclined modular photobioreactor for outdoor mass cultivation of photoautotrophs. Biotechnology and Bioengineering 1996;51:51–60.
[24]. Molina Grima E, Belarbi E, Acie´nFerna´ndez F, Robles Medina A, Chisti Y. Recovery of microalgal biomass and metabolites: process options and economics. Biotechnology Advances 2003;20:491–515.
[25]. Chen L, Li P, Liu Z, Jiao Q. The released polysaccharide of the cyanobacterium Aphanothecehalophytica inhibits flocculation of the alga with ferric chloride. Journal of Applied Phycology 2008;1–5.
[26]. Benemann J, Kopman B, Weissman D, Eisenberg D, Goebel R. Development of microalgae harvesting and high rate pond technologies in California. Algal Biomass 1980;457.
[27]. Mohn F. Experiences and strategies in the recovery of biomass from mass cultures of microalgae. Algae Biomass 1980;547–71
[28]. Balasundaram B, Harrison S, Bracewell DG (2009) Advances in product release strategies and impact on bioprocess design. Trends Biotechnol 27: 477-485.
[29]. Ledung E, Eriksson PO, Oscarsson S (2009) A strategic crossflow filtration methodology for the initial purification of promegapoietin from inclusion bodies. J Biotechnol 141: 64-72.
[30]. Xu Y, Zhang L, Yao W, Yedahalli SS, Brand S et al. (2009) Bioprocess development for production, purification, and structural characterization of recombinant hCD83ext as a potential therapeutic protein. Protein Expr Purif 65: 92-9.
[31]. Huang TK, Plesha MA, Falk BW, Dandekar AM, McDonald KA (2009) Bioreactor strategies for improving production yield and functionality of a recombinant human protein in transgenic tobacco cell cultures. BiotechnolBioeng 102: 508-520.
[32]. Kalbfuss B, Flockerzi D, Seidel-Morgenstern A, Reichl U (2008) Size-exclusion chromatography as a linear transfer system: purification of human influenza virus as an example. J Chromatogr B Analyt Technol Biomed Life Sci 873: 102-12.
[33]. Rani R, Ghosh S (2011) Production of phytase under solid-state fermentation using Rhizopus oryzae: novel strain improvement approach and studies on purification and characterization. Bioresour Technol 102: 10641-10649
[34]. Rayat AC, Micheletti M, Lye GJ (2010) Evaluation of cell disruption effects on primary recovery of antibody fragments using microscale bioprocessing techniques. Biotechnol Prog 26:1312-1321.
[35]. Zhao G, Song S, Wang C, Wu Q, Wang Z (2011) Determination of triazine herbicides in environmental water samples by high-performance liquid chromatography using graphene-coated magnetic nanoparticles as adsorbent. Anal Chim Acta 708: 155-159.
[36]. Hirayama A, Soga T (2011) Amino Acid analysis by capillary electrophoresismass spectrometry . Methods Mol Biol 828: 77-82.
[37]. Maher HM, Sultan MA, Olah IV (2011) Development of validated stabilityindicating chromatographic method for the determination of fexofenadine hydrochloride and its related impurities in pharmaceutical tablets. Chem Cent J 5:76.
[38]. Porel A, Haty S, Kundu A (2011) Stability-indicating HPLC Method for Simultaneous Determination of Terbutaline Sulphate, Bromhexine Hydrochloride and Guaifenesin. Indian J Pharm Sci 73: 46-56.
[39]. Salazar C, Armenta JM, Cortés DF, Shulaev V (2011) Combination of an AccQ·Tag-Ultra Performance Liquid Chromatographic Method with Tandem Mass Spectrometry for the Analysis of Amino Acids. Methods Mol Biol 828: 13-28.
[40]. McCue JT, Selvitelli K, Walker J (2009) Application of a novel affinity adsorbent for the capture and purification of recombinant factor VIII compounds. J Chromatogr A 1216: 7824-7830.
[41]. Mednis M, Meitalovs J, Vilums S, Vanags J, Galvanauskas V. Bioprocess monitoring and control using mobile devices. Inf Technol Control. 2010;39:195–201. https://doi.org/10.5755/j01.itc.39.3. 12369.
[42]. Rathore AS, Kateja N, Agarwal H. Part fve continuous downstream bioprocessing. Contin Biomanufacturing Innov Technol Methods Innov Technol Methods. 2017; 261–279

[43]. Knospe C. PID control. IEEE Control Syst. 2006;26:30–1. https:// doi.org/10.1109/MCS.2006.1580151.
[44]. Tatjewski P. Advanced control of industrial processes: structures and algorithms. 2007. http://www.springer.com/engineering/ control/book/978-0-85729-634-4%0A. https://books.google.com/ books?hl=en&lr=&id=e_QEnZB0PLoC&pgis=1.
[45]. Barker M, Rawtani J, Mackay S. Batch control technologies. Pract Batch Process Manag. 2005. https://doi.org/10.1016/b978-07506 6277-2/50011-6.
[46]. Hopkins D, St Amand M, Prior J. Bioreactor automation. Man Ind MicrobiolBiotechnol. 2014. https://doi.org/10.1128/9781555816827.ch51.
[47]. Faedo NE, Lucero M, Mazzone V, Suarez M, Rojas NL. Low cost SCADA for a laboratory-scale bioreactor, 2015 16th Work. Inf Process Control RPIC 2015. 2016. Doi: https://doi.org/10.1109/ RPIC.2015.7497090.
[48]. Mesquita TJB, Sargo CR, Fuzer JR, Paredes SAH, Giordano RDC, Horta ACL, Zangirolami TC. Metabolic fuxes-oriented control of bioreactors: a novel approach to tune micro-aeration and substrate feeding in fermentations. Microb Cell Fact. 2019. https://doi.org/ 10.1186/s12934-019-1198-6.
[49]. Kornecki M, Strube J. Process analytical technology for advanced process control in biologics manufacturing with the aid of macroscopic kinetic modeling. Bioengineering. 2018. https://doi.org/10.3390/bioengineering5010025.
[50]. Rani KY, Rao VSR. Control of fermenters—a review. Bioprocess Eng. 1999;21:77–88. https://doi.org/10.1007/s004490050644.