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An Overview on Design of Experiment in Product Formulation

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ABSTRACT

The pharmaceutical product development process requires specific domain knowledge and expertise in specific area. Design of Experiment is a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management.

Keywords: Design of Experiment, Product Formulation, Drug-Excipients, Tablet Granulation, Dissolution testing

INTRODUCTION

A drug candidate must be chemically, physically stable and manufacturable throughout the product life cycle and manufacturing process,). In addition, many quality standards and special requirements must be met to ensure the efficacy and safety of the product. It is always essential to establish the (target product profile) TPP so that the formulation effort will be effective and focused [1,2]. The TPP usually includes dosage form, route of administration, special-delivery requirement, maximum and minimum doses, and aspects of pharmaceutical elegance (appearance). The TPP guides formulation scientists to establish formulation strategies [3-12] and keep formulation effort focused and efficient. After the TPP is clearly defined, many studies must be conducted to develop a formulation. DOE is an effective tool for formulation scientists throughout the many stages of the formulation process and can help scientists make intelligent decisions. These steps include optimization of product, drug-excipient compatibility [13-19], process feasibility studies, formulation, and scale-up, and characterization of manufacturing process.

DESIGN OF EXPERIMENT

Design of Experiment [20-22] is a systemic approach to determine the relation between independent process/product variable and their effect on response variable **(Figure 1).**

Terminology used in Design of Experiment

1. Independent Variables: These variables are directly under the control of formulation scientist
2. Dependent variables: These variables are result or response
3. Factors: There are two types of factors are there Qualitative and Quantitative factors
4. Level: These are the values assigned or designated for factors
5. Responses surface plot: A 3-D graphical representation between independent factor and dependent factor
6. Interaction: It gives the overall effect of two or more variables means lack of additivity of factor effects
7. Effect: Magnitude in change in response

8. Contour plot: These are two dimensional representation of response obtained by plotting one independent variable against another keeping the response and other variable constant
9. Contour lines: curves obtained over counter plot to a response value
10. MLRA (Multiple Linear Regression Analysis): The technique which express mathematically in form of quadratic equation the linear relationship between various independent variable and dependent variable (Response)
11. Orthogonality: When effect is due to the main factor of interest and no interaction
12. Confounding: Lack of Orthogonality is termed as confounding or aliasing
13. Resolution: Measurement of degree of confounding

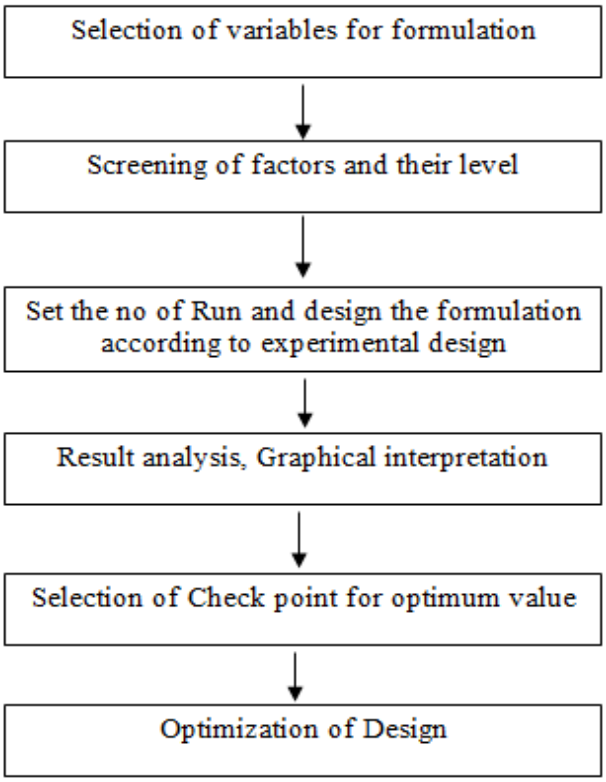

Figure 1: Flow Chart in Design of Experiment.

Types of Experimental Design

A. Completely randomized designs.
B. Full Factorial designs.
- Two-level full factorial designs.
- Full factorial example.
- Blocking of full factorial designs.

C. Fractional factorial designs.
- A 23-1 half-fraction designs.
- How to construct 23-1 designs.
- Confounding.
- Design resolution.
- Use of fractional factorial designs.
- Screening designs.
- Fractional factorial designs summary tables.

D. Randomized block designs.
- Latin squares.
- Graeco-Latin squares.
- Hyper-Graeco-Latin squares.

E. Plackett-Burman designs.
F. Response surface (second-order) designs.
- Central composite designs.
- Box-Behnken designs.
- Response surface design comparison.
- Blocking a response surface design.

G. Adding center points.
H. Improving fractional design resolution.
- Mirror-image foldover designs.
- Alternative foldover designs.

I. three-level full factorial designs.
J. Three-level, mixed level and fractional factorial designs

Application of Experimental Design

- Compatibility studies between Drug-Drug [23] and Drug-Excipients
- Granulation
- Pre Tablet Granulation [24-29]
- Oral-controlled release formulation [30-33]
- Modelling of properties of powder [34-41]
- Dissolution testing [42-62]
- Tablet formulation [63-78]
- Coating of tablets
- Extrusion-Spheronization
- Inhalation formulation [79-90]

Software used in Experimental Design

- DESIGN EXPERT
- FACTOP
- OPTIMA
- XTAP
- OMEGA
- ECHIP
- MULTI-SIMPLEX
- NEMRODW
- GRAPHPAD PRISM
- DoE PC IV
- MINITAB
- MODDE

CONCLUSION

Over the past decade the practice of optimization of formulation has increased. DoE optimization would further gain increased acceptance as a priceless developmental tool. DOE is an effective tool for formulation scientists starting from pre-formulation stage to various stages of clinical trial in product development. What is essentially needed for realization of this quality breakthrough is the workable basic knowledge of computers and statistics, coupled with persistence, patience, perseverance and passion. Different techniques used in optimization [91-100] mainly reduces the number of trial thereby cost and time consumed in product development.

REFERENCES

1. Anil Vaidya. Drug Designing and Development: Emerging Role of Health Technology Assessment. Drug Des. 2014;3:111.
2. Barakat K. Computer-Aided Drug Design. J Pharma Care Health Sys. 2014;1:e113.
3. Abdou EM and Ahmed NM. Terconazole Proniosomal Gels: Effect of Different Formulation Factors, Physicochemical and Microbiological Evaluation. J Pharm Drug Deliv Res. 2016;5:1.
4. Strehlow B, et al. A Novel Microparticulate Formulation with Allicin In Situ Synthesis. J Pharm Drug Deliv Res. 2016;5:1.
5. Nair AK, et al. Development and Comparative Assessment of Hydrocolloid Based Against Wax Based Gastro Retentive Bilayered Floating Tablet Designs of Atorvastatin Calcium Using Qbd Approach. J Pharm Drug Deliv Res. 2015;4:3.
6. Satyavathi K, et al. Formulation and In-Vitro Evaluation of Liposomal Drug Delivery System of Cabazitaxel. J Pharm Drug Deliv Res. 2015;4:2.
7. Panchangam RBS and Dutta T. Engineered Nanoparticles for the Delivery of Anticancer Therapeutics. J Pharm Drug Deliv Res. 2015;4:1.
8. Redasani VK, et al. Development and Validation of Spectroscopic Methods for the Estimation of Mupirocin Calcium in Bulk and in Ointment Formulation. J Forensic Toxicol Pharmacol. 2015;4:2.
9. Naik DR, et al. Release Kinetics of Cellulosic Nano particulate Formulation for Oral Administration of an Antiviral Drug: Effect of Process and Formulation variables. J Pharm Sci Emerg Drugs. 2014;2:1.
10. Poda AR, et al. Nano-Aluminum Thermite Formulations: Characterizing the Fate Properties of a Nanotechnology during Use. J Nanomater Mol Nanotechnol. 2013;2:1.
11. Sharma B, et al. Formulation, Optimization and Evaluation of Atorvastatin Calcium Loaded Microemulsion. J Pharm Drug Deliv Res. 2012;1:3.
12. Kipping T and Rein H. Development of Extruded Starch Based Formulations Aimed for Local Drug Delivery to Oral Cavity. J Pharm Drug Deliv Res. 2012;1:1.
13. Monajjemzadeh F. LC-Mass as a Complementary Method in Detecting Drug-Excipient Incompatibility in Pharmaceutical Products. J Mol Pharm Org Process Res. 2014;2:e110.
14. Meier-Davis SR, et al. Enhancing the Skin Flux of Tolnaftate Utilizing the Novel Excipient, Dodecyl-2-N,N-Dimethylaminopropionate (DDAIP). J Pharm Drug Deliv Res. 2012;1:1.
15. Anumolu PD, et al. Gas Chromatographic Assessment of Residual Solvents Present in Excipient-Benzyl Alcohol. J Chromatogr Sep Tech. 2016;7:321.
16. Chauhan H. Selection of Polymeric Excipients for Poorly Soluble Drugs. J Develop Drugs. 2015;4:e140.
17. Monajjemzadeh F. LC-Mass as a Complementary Method in Detecting Drug-Excipient Incompatibility in Pharmaceutical Products. J Mol Pharm Org Process Res. 2014;2:e110.
18. Debar S, et al. The Novel Excipient, Dodecyl-2-N, N-dimethylaminopropionate Hydrochloride (DDAIP-HCl) Improves the Flux of Minoxidil in Human Skin. Hair Ther Transplant. 2012;2:105.
19. Ogaji IJ, et al. Advances in Natural Polymers as Pharmaceutical Excipients. Pharm Anal Acta. 2012;3:146.
20. Abdallah I, et al. Simultaneous Determination of Atenolol and Nifedipine by Using Spectrophotometric Method with Multivariate Calibration and HPLC Method Implementing “Design of Experiment”. Pharm Anal Acta. 2015;6:384.
21. Agrahari V, et al. Application of Design of Experiment and Simulation Methods to Liquid Chromatography Analysis of Topical HIV Microbicides Stampidine and HI443. J Anal Bioanal Tech. 2014;5: 180.
22. Sharma S and Rana RS. Optimization of Mechanical Behaviour of AA 5083 Nano Sic Composites Using Design of Experiment. J Material Sci Eng. 2015;4: 176.
23. Suresh Babu VV, et al. Validated HPLC Method for Determining Related Substances in Compatibility Studies and Novel Extended Release Formulation for Ranolazine. J Chromatograph Separat Techniq. 2014;5:209.
24. Nair AK, et al. Development and Comparative Assessment of Hydrocolloid Based Against Wax Based Gastro Retentive Bilayered Floating Tablet Designs of Atorvastatin Calcium Using Qbd Approach. J Pharm Drug Deliv Res. 2015;4:3.
25. Efentakis M and Siamidi A. Design and Evaluation of a Multi Layer Tablet System Based on Dextran. J Pharm Drug Deliv Res. 2014;3:2.
26. Malvey S, et al. Formulation and Evaluation of Acyclovir Orodispersible Tablets Using Sublimation Method. J en Pract. 2015;3:208.
27. Zack J, et al. Bioequivalence of the Rilpivirine/Emtricitabine/Tenofovir Alafenamide Single-Tablet Regimen. J Bioequiv Availab. 2016;8:049-054.
28. Gul S and Sajid S. Formulation of Improved Norfloxacin HCl Tablets: Quality Control Assessment and Comparison Study of Acidic and Basic Form of Norfloxacin in Tablet Formulation. J Develop Drugs. 2015;5:145.

29. Kubo Y, et al. Interventional Evaluation of Monoammonium Glycyrrhizinate-Glycine/DLMethionine Combination Tablets in Mild Alopecia Areata. J Clin Exp Dermatol Res. 2016;7:322.
30. Pawar HA and Yadav A. Development and Application of Rp-Hplc Method for Dissolution Study of Oral Formulations Containing Amlodipine Besylate. Pharm Anal Acta. 2015;6:437.
31. Sallam A, et al. Bioequivalence of Two Oral Formulations of Modafinil Tablets in Healthy Male Subjects under Fed and Fasting Conditions. J Bioequiv Availab. 2015;7:063-067.
32. Bartoli AN, et al. Bioavailability of a New Oral Spray Melatonin Emulsion Compared with a Standard Oral Formulation in Healthy Volunteers. J Bioequiv Availab. 2012;4:096-099.
33. César IC, et al. Bioequivalence Study of Two Oral Formulations of Memantine Tablets in Healthy Brazilian Volunteers after a Single Dose Administration. J Bioequiv Availab. 2012;4:014-017.
34. Bhattacharya SS, et al. Process Validation of Ceftriaxone and Sulbactam Dry Powder Injection. J Chem Eng Process Technol. 2014;5:211.
35. Kuehl PJ, et al. Development and Validation of an HPLC Assay For Dual Detection of Gentamicin Sulfate and Leucine From a Novel Dry Powder For Inhalation. J Anal Bioanal Tech. 2012;3:152.
36. Kuehl PJ, et al. Development and Validation of an HPLC Assay For Dual Detection of Gentamicin Sulfate and Leucine From a Novel Dry Powder For Inhalation. J Anal Bioanal Tech. 2012;3:152.
37. Wang W, et al. The Protection Potential of an Alum-Adjuvanted F1 Protein in Dry Powder against Plague in Mice. J Vaccines Vaccin. 2010;1:105.
38. Amini A. Identification of Ɛ-Caprolactam and Melamine in Polyvinyl-Pyrrolidone Powder by Double Injection Micellar Elektrokinetic Chromatography.Pharm Anal Acta. 2015;6:442.
39. Mahmoud MA. Thermodynamics and Kinetics Studies of Mn (II) Removal from Aqueous Solution onto Powder Corn Cobs (PCC). J Chromatogr Sep Tech. 2015;6:301.
40. Yu PV, et al. The Co-Grinding of Z/Cao/$Al(OH)_3$(Z=ZnO Or $Zn_4CO_3(OH)_6$) Powder Compositions as Technique for Preparation of Sorbents. J Material Sci Eng. 2015;4:195.
41. Elhassan GO, et al. Preparation and In Vitro Characterization of Artemisinin Freeze-Dried Powders with Various Carriers. J Pharmacovigil. 2015;3:156.
42. Qureshi SA. A Critical Assessment of Current Practices of Drug Dissolution Testing – Irrelevancies, their Causes and Suggestions to Address These. J App Pharm. 2015;8:208.
43. Tzanavaras PD. Sequential Injection Analysis: A useful Analytical Tool in Drug Dissolution Testing. Pharmaceut Anal Acta. 2012;3:e114.
44. Lahdenperä E and Koiranen T. A Novel Manufacturing Method for Sustained Release Products and Modelling Dissolution. J Thermodyn Catal. 2016;7:159.
45. Yang X, et al. Nonequilibrium Dissolutiondiffusion Model for PDMS Membrane Pervaporation of ABE Water Binary System. J Membra Sci Technol. 2016;6:143.
46. Myint HH, et al. Dissolution Model of Ball Milled Rice Straw Particles in 1-Ethyl-3-Methyl Imidazolium Acetate at Elevated Temperature. J Bioprocess Biotech. 2015;5:260.
47. Pawar HA and Yadav A. Development and Application of Rp-Hplc Method for Dissolution Study of Oral Formulations Containing Amlodipine Besylate. Pharm Anal Acta. 2015;6:437.
48. Brijesh KV, et al. Physicochemical Characterization and In-Vitro Dissolution Enhancement of Bicalutamide-Hp-B-Cd Complex. J Pharm Drug Deliv Res. 2015;3:2.
49. Satya Krishna HP, et al. Solubility and Dissolution Enhancement of Candesartan Cilexetil by Liquisolid Compacts. J Pharm Drug Deliv Res. 2013;2:2.
50. Agatonovic-Kustrin S, et al. Biorelevant Dissolution Studies of Pioglitazone HCL Immediate Release Tablets and the Determination of an In Vitro In Vivo Correlation. J Bioequiv Availab. 2015;7:086-089.
51. Kakran M, et al. Fabrication of Nanoparticles of Silymarin, Hesperetin and Glibenclamide by Evaporative Precipitation of Nanosuspension for Fast Dissolution. Pharm Anal Acta. 2015;6:326.
52. Saeed Arayne M, et al. Monitoring of Pregabalin in Pharmaceutical Formulations and Human Serum Using UV and RPHPLC Techniques: Application to Dissolution Test Method. Pharm Anal Acta. 2014;5:287.
53. Tsume Y, et al. Dissolution Effect of Gastric and Intestinal pH fora BCS class II drug, Pioglitazone: New in vitro Dissolution System to Predict in vivo Dissolution. J Bioequiv Availab. 2013;5:224-227.
54. Jethara SI and Patel MR. Enhanced Solubility and Dissolution Rate of Aceclofenac by Using Spray Drying Techniques. Intel Prop Rights. 2015;3:140.
55. Lewis DR and Liu DJ. Direct Measurement of Lipase Inhibition by Orlistat Using a Dissolution Linked In Vitro Assay. Clinic Pharmacol Biopharm. 2012;1:103.
56. Tzanavaras PD. Sequential Injection Analysis: A useful Analytical Tool in Drug Dissolution Testing. Pharmaceut Anal Acta. 2012;3:e114.
57. Ali S and Ali AS. Determination of Thermodynamic Parameters from the Dissolution of Calcium Hydroxide in Mixed Solvent Systems by pH-Metric Method. J Phys Chem Biophys. 2013;3:116.
58. Nanjwade BK, et al. Effect of Compression Pressure on Dissolution and Solid State Characterization of Cefuroxime Axetil. J Anal Bioanal Tech. 2010;1:112.

59. Jamadar LD, et al. Comparison of us and Japanese Regulations for Invivo Dissolution and Invivo Bioequivalence Studies. J Bioanal Biomed. 2010;2:017-022.
60. Shakeel F, et al. Solubility and Dissolution Improvement of Aceclofenac using Different Nanocarriers. J Bioequiv Availab. 2009;1:039-043.
61. Somagoni J, et al. Preparation of Inclusion Complexes of Amlodipine Base and its Besylate and Maleate Salts with Hydroxy Propyl ß -cyclodextrin -A study on Stereospecific Dissolution. Pharm Anal Acta. 2011;2:123.
62. Nanjwade BK, et al. Design and Characterization of Nanocrystals of Lovastatin for Solubility and Dissolution Enhancement. J Nanomedic Nanotechnol. 2011;2:107.
63. Gul S and Sajid S. Formulation of Improved Norfloxacin HCl Tablets: Quality Control Assessment and Comparison Study of Acidic and Basic Form of Norfloxacin in Tablet Formulation. J Develop Drugs. 2015;5:145.
64. Rajurkar VG, et al. Tablet Formulation and Enhancement of Aqueous Solubility of Efavirenz by Solvent Evaporation Co- Crystal Technique. Med chem. 2015;S2:002.
65. Ponce-Navarrete D, et al. Bioavailability of Two Different Tablet Formulations of Telmisartan of Two Different Strengths (40 mg and 80 mg) in Healthy Male Mexican Volunteers. J Bioequiv Availab. 2015;7:164-169.
66. Marín LE, et al. Bioequivalence of Two Oral Tablet Formulations of Betahistine 24 Mg: Single-Dose, Open-Label, Randomized, Two-Period Crossover Comparison in Healthy Individuals. J Bioequiv Availab. 2015;7:001-004.
67. Tamayo GM, et al. Bioavailability of Two Tablet Formulations of a Single Dose of Moxifloxacin 400 mg: An Open-Label, Randomized, Two-Period Crossover Comparison in Healthy Mexican Adult Volunteers. J Bioequiv Availab. 2014;6:197-201.
68. Zhao Q, et al. Relative Bioavailability of a Fixed-Combination Tablet Formulation of Azithromycin and Chloroquine in Healthy Adult Subjects. J Bioequiv Availab. 2013;5: 001-005.
69. Wagh N, et al. A Bioequivalence Study of Two Finofibrate Tablet Formulations in Indian Healthy Subjects. J Bioequiv Availab. 2013;5: 016-021.
70. Harahap Y, et al. Bioequivalence of Trimetazidine Modified Release Tablet Formulations Assessed in Indonesian Subjects. J Bioequiv Availab. 2013;5:117-120.
71. Damle B, et al. Bioequivalence of Alprazolam Sublingual Tablet Formulation and Alprazolam Immediate Release Tablet in Healthy Volunteers. J Bioequiv Availab. 2013;5:149-153.
72. Shatti LAA. Method Development and Validation of Assay of Chlorpromazine Hydrochloride Tablet Formulation Using Ultra Violet Visible Spectrophotometry. J Anal Bioanal Tech. 2014;5:186.
73. Zhang J, et al. Pharmacokinetics and Bioequivalence Comparison of 600 mg Single-Dose Linezolid Oral Suspension and Tablet Formulation in Healthy Chinese Subjects. J Bioequiv Availab. 2014;6:153-157.
74. Behera S, et al. UV-Visible Spectrophotometric Method Development and Validation of Assay of Paracetamol Tablet Formulation. J Anal Bioanal Tech. 2012;3:151.
75. Harahap Y, et al. A Bioequivalence Study of Two Azithromycin Tablet Formulations in Indonesian Healthy Subjects. J Bioequiv Availab. 2012;4:048-051.
76. Hernandez E, et al. Bioavailability of Two Different Coated-Tablet Formulations of Valacyclovir of Two Different Strengths (500 mg and 1000 mg) in Healthy Mexican Adult Volunteers. J Bioequiv Availab. 2012;4:035-039.
77. Balderas-Acata JI, et al. Bioavailability of Two Coated- Tablet Formulations of a Single Dose of Pantoprazole 40 mg: An Open-Label, Randomized, Two-Period Crossover, Comparison in Healthy Mexican Adult Volunteers. J Bioequiv Availab. 2011;3:077-081.
78. Prabu SL, et al. Simultaneous Determination of Gatifloxacin and Ambroxol Hydrochloride in a Tablet Formulation by Liquid Chromatography. Pharm Anal Acta. 2010;1:110.
79. Dilhan M Kalyon, et al. Functionally-Graded Polymeric Graft Substitutes and Scaffolds for Tissue Engineering can be Fabricated via Various Extrusion Methods. J Tissue Sci Eng. 2014;5:e128.
80. Kalyon DM, et al. Twin Screw Extrusion Based Technologies Offer Novelty, Versatility, Reproducibility and Industrial Scalability for Fabrication of Tissue Engineering Scaffolds. J Tissue Sci Eng. 2013;4: e126.
81. Imran M, et al. Influence of Extrusion Processing on Fatty acids Retention in Full-fat Flaxseed (Linum usitatissimum L.) Meal. J Food Process Technol. 2013;4:268.
82. Myat L and Ryu GH. Extrusion with Thermostable α-amylase Injection as Pretreatment Method for Ethanol Production from Corn Starch. J Microb Biochem Technol. 2013;5:047-053.
83. Hamza RG, et al. Effect of Gamma- Irradiation or/and Extrusion on the Nutritional Value of Soy Flour. Biochem Anal Biochem. 2012;1:118.
84. Lin Z, et al. Screw Extrusion Pretreatments to Enhance the Hydrolysis of Lignocellulosic Biomass. J Microb Biochem Technol. 2012;S12:002.
85. Akhtar J and Khan MA. Extruded Pet Food Development from Meat Byproducts using Extrusion Processing and its Quality Evaluation. J Food Process Technol. 2015;7:539.

86. Sobowale SS, et al. Effect of Extrusion Variables on the Extrudate Properties of Wheat-plantain Noodle. J Food Process Technol. 2016;7:547.
87. Tovar JX, et al. Microstructure of a Third Generation Snack Manufactured by Extrusion from Potato Starch and Orange Vesicle Flour. J Food Process Technol. 2016;7:563.
88. Maskus H and Arntfield S. Extrusion Processing and Evaluation of an Expanded, Puffed Pea Snack Product. J Nutr Food Sci. 2015;5:378.
89. Tunsophon S and Nemere I. Role of PKCb in Signal Transduction for the 1,25D3-MARRS Receptor (ERp57/PDIA3) in Steroid Hormone-Stimulated Calcium Extrusion. Anat Physiol. 2011;S1:002.
90. Ukuku DO, et al. Behavior of Escherichia coli Bacteria in Whey Protein Concentrate and Corn Meal During Twin Screw Extrusion Processing at Different Temperatures. J Food Process Technol. 2012;3:150.
91. Verma AK and Leekha A. Elucidation of Glutathione-S-transferase Activity Induced by Pectin-Cisplatin Nano-conjugates for Optimization of New Therapeutic Strategies. J Nanomed Nanotechnol. 2016;7:391.
92. Madhavi K, et al. Preparation, Optimization and Characterization of Eudragit Coated Chitosan Piroxicam Microspheres Intended for the Treatment of Rheumatoid Arthritis. Pharm Anal Acta. 2016;7:485.
93. Abdellatif AAH, et al. A Formulation, Optimization and Evaluation of Controlled Released Alginate Beads Loaded-Flurbiprofen. J Nanomed Nanotechnol. 2016;7:357.
94. Javaid MA, et al. Optimization of Operational Conditions for Maximum Biodecolorization of Orange C2RL Dye. J Bioremed Biodeg. 2016;7:324.
95. Oliveira SC, et al. Kinetic Modeling and Optimization of a Batch Ethanol Fermentation Process. J Bioprocess Biotech. 2016;6:266.
96. Sharma M, et al. Denovo Designing, Virtual Screening and Lead Optimization of Potential Drug Candidate for Herpes Disease. J Microb Biochem Technol. 2015;7:367-373.
97. Kieu HTQ, et al. Optimization of Culture Conditions for Hydrogen Production by an Anaerobic Bacteria Strain on Soluble Starch Using Response Surface Methodology. J Bioprocess Biotech. 2015;5:265.
98. Lugani Y, et al. Optimization of Cellulase Production from Newly Isolated Bacillus sp. Y3. J Bioprocess Biotech. 2015;5:264.
99. Lim SJ. Optimization of Removing Organic Matter and Nutrient using Advanced Oxidation Processes and On-line Monitoring systems. J Bioremed Biodeg. 2015;6:e169.
100. Guermazi Z, et al. Characterization of Extra Virgin Olive Oil Obtained from Whole and Destoned Fruits and Optimization of Oil Extraction with a Physical Coadjuvant (Talc) Using Surface Methodology. J Anal Bioanal Tech. 2015;6:278.