e-ISSN: 2320-1215
p-ISSN: 2322-0112

Research and Reviews: Journal of Pharmacy and Pharmaceutical Sciences

Formulation Development and Evaluation of Bi-Layer Sustained Release Tablets of Amlodipine and Metaprolol

Sindhu P[1], Madhu Babu Sakshi[2]*, M.Trinadha Rao[2]

[1]Department of Pharmacy, Vaageswari institute of pharmaceutical sciences, Thimapur, Karimnagar, Telangana, India
[2]Department of Pharmaceutics, Vignan Institute of Pharmaceutical Technology, Beside VSEZ, Duvvada, Visakhapatnam-530 046, AP, India

Review Article

Received: 19/04/2014
Accepted: 21/05/2014
Published: 27/05/2014

***For Correspondence**

Corresponding author's affiliation:

Madhu Babu Sakshi, M. Pharmacy, Department of Pharmaceutics, Vignan institute of Pharmceutical sciences, Visakhapatnam, Andhra Pradesh, India, Tel: 9491375747; E-mail: sakshi.madhu@gmail.com
Sindhu P, B-pharmacy, Vaageswari institute of pharmaceutical sciences, Thimapur, karimnagar, Telgana, India, Tel: 8121474344; E-mail: sindhureddy.pingili@gmail.com

Keywords: Bilayer tablets; Amlodipine besylate; Metoprolol succinate; Sustained release; Immediate release; Antihypertension; Combination therapy

ABSTRACT

Background and Objective: The objective of the present research, an attempt has been made to formulate bilayered tablets of Amlodipine besylate and Metoprolol succinate. The main objective for combination therapy is to encourage the use of lower doses of drug to reduce the patient's blood pressure, to minimize dose dependent side effects and adverse reactions. When smaller doses of medication with different mechanism of action are combined, synergistic or additive effects on blood pressure are achieved.

Methods: Nine different formulations of bilayered tablets were prepared with Amlodipine besylate as immediate release layer and Metoprolol succinate as Sustained release layer. Tablets were prepared by direct compression technique. Immediate release layer was prepared by using Super desintegrant CCS. Sustained release layer was prepared by different ratios of polymers like HPMC K100M, Acacia and Combination of both. The prepared tablets were evaluated for pre and post compression parameters, drug content, in vitro dissolution studies and stability studies.

Results: All the evaluated parameters of the optimized formulation optimized formula showed the metaprolol succinate drug release over a period of 16 to 20 hours.and the amlodipine besilate (IR) release the max drug in 60 minutes showed compliance with pharmacopoeial standards.

Interpretation and conclusion: The optimized formulation of bilayer tablets showed good release profile and are within pharmacopoeial limits. The extended release Metoprolol layer of optimized formulation follows first order and shows non-Fickian diffusion mechanism of release this formulation was subjected to stability studies. The stability studies were carried out for the optimized batch for three months and it showed acceptable results.

Introduction

In the recent days, multilayer tablets occupying the importance in the designing of oral control drug delivery systems. Bi-layer tablets are prepared with one layer of drug for immediate release while second layer designed to release drug later, either as second dose or in an sustained release manner. Bilayer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances, and also for sustained release tablet in which one layer is immediate release as initial dose and second layer is maintenance dose. The combination therapy is to encourage the use of minimize the dose dependent side effect and adverse reactions, decreasing dosing frequency [1-6].

e-ISSN: 2320-1215
p-ISSN: 2322-0112

Metaprolol succinate is a widely used ß1 selective adreno receptor antagonist,is rapidly and completely absorbed from the gastrointestinal track when administration in conventional dosage forms.The systemic availabity after oral administered in , however , is only about 50%due to hepatic oxidative metabolism which is subjected to genetic polymorphism. Since metaprolol has a relatively short elimination halflife of 3-4hours having bioavailabity(12%),a simple once daily dosage regimen of a conventional tablet is not sufficient to sustain plasma levels and clinically effective ß1 blockade over the entire day. For the patient compliance the metaprolol succinate as sustained release is necessary [7-13].
Amlodipine is a prototype second generation dihydropyridine calcium channel blocker that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. It has a longer duration of action (ie) halflife of 40 hours having bioavailabity (64-90%), and the initial effects are cumulative over many days and more over for patient compliance in case of anti-angina patients, a rapid onset of action is necessary for immediate pain relief. Hence Amlodipine can be given as a single immediate release dose [14-21].

Formulation of Bi-Layer Sustained Release Tablets

Amlodipine besylate , Metaprolol succinate Mylan Laboratories, Hyderabad ,Crosscarmellose sodium, Sunset yellow ,Pvp k 30 , Acacia gum , Dicalcium phosphate ,Hpmck100m, Yarrow Chem. Products, Mumbai, Magnesium stearate , Talc ,Molychem, Mumbai.

Preparation of Amlodipine besylate immediate release layer: Amlodipine is a hygroscopic material. Being an unstable compound, Amlodipine requires well directed stability approaches to formulate Amlodipine layer with reasonable stability. Hence Amlodipine layer (immediate release layer) was prepared by direct compression method.

Shifting: Amlodipine Besylate, Dicalcium phosphate and sodium starch glycolate were shifted through ♯ 40 mesh. Magnesium Stearate was sifted through ♯ 60 mesh sieves. Sunset yellow lake was sifted through ♯ 100 mesh sieve [21-27].
Blending: Mix geometrically Amlodipine with Dicalcium phosphate, ccs and Sunset yellow lake. Mix for 15 minutes in double lined polybag.
Lubrication: The above blend was lubricated with Magnesium Stearate for 2 minutes.
Preparation of Metoprolol succinate sustained release layer: Metoprolol layer (sustained release layer) was prepared by direct compression method.
Sifting: Sift Metoprolol Succinate through ♯ 30 mesh sieve, Dicalcium phosphate HPMC K100m, pvp k30 through ♯ 40 mesh
Blending: Blended Metoprolol Succinate andDicalcium phosphate, acacia, and HPMC K 100M, in a double cone blender for 20 minutes [27-28].

Tablet compression:

The bilayer tablet compression was made using mm punch in a 6 station rotary tablet machine with single feed. In this, sustained release metoprolol succinate granules were introduced first in to the die cavity and a slight precompression was made so that the layer was uniformly distributed. After that immediate release amlodipine besilate granules were added through the feed and a final compression was made [29-33].

Characterization and evaluation of bilayered tablets

Pre compression parameters

Evaluation of powder blend for the bulk density, tapped density, Carr's index, Hausner's ratio and angle of repose. The results were optimized.
Post compression parameters: Tablets were tested for hardness, friability and weight variation. Thickness, of the tablets was determined by using digital vernier callipers.
Hardness of the tablets was tested using Monsanto hardness tester and friability of the tablets was determined in a Roche friabilator [34-40].

e-ISSN: 2320-1215
p-ISSN: 2322-0112

Invitro dissolution study: For Amlodipine besylate (IR): Dissolution parameters: Dissolution studies for amlodipine besylate were performed by using Medium: 0.1 N HCL Volume : 900 ml using dissolution apparatus type II of USP (paddle)(LABINDIA DS 8000) With Rotating speed : 50 rpm andTemperature : 370C± 0.50 C. samples of dissolution fluids were withdraw through a filter (0.45 µm) at Time intrewels 10, 20, 30, 45, and 60 Min. And the dissolution sample fluids were analysed by spectrophotometrically at 237 nm using UV Visible Spectrophotometer (ELICO SL 159).For amlodipine besilate drug content [41-50].

For metaprolol succinate (SR): Dissolution studies were performed by using 6.8ph buffer 900ml volume using dissolution apparatus type II of USP (paddle)(LABINDIA DS 8000) With Rotating speed : 50 rpm andTemperature : 370C ± 0.50 C. samples of dissolution fluids were withdraw through a filter (0.45 µm) at Time intrewels 1,2,4,8,12,16,20 hours. And the dissolution sample fluids were analysed by spectrophotometrically at 222nm using UV Visible Spectrophotometer (ELICO SL 159). For metaprolol succinate drug content [51-57].

Results and Discussion

Bilayerd tablets of Metoprolol Succinate, and amlodipine besilate were Metaprolol succinate (SR) prepared by using different polymer like HPMC□K100M, Acacia, both combnation of HPMC-K100M+acacia in the ratio 1:1. For Amlodipine (IR) CCS used as asuper diesintegrant. The tablets were fabricated using direct compression technique. The pre blended powders of the sustained release layer and the immediate release were characterized and the parameters were showed in the table . Content uniformity of all the prepared batches is within the limit (amlodipine besilate, and metaprolol succinate 100 ± 3% of the labelled content) [58-68]. The pre compression parameters and other post compressed parameters of tablets friability, hardness, weight variation and thickness are optimized [69-78]. We can conclude that all the batches of tablets prepared were of good quality with regard to hardness, friability and drug content [79-83].

In vitro dissolution study for amlodipine besilate (IR)

The in vitro drug release profiles of Amlodipine besilate were obtained. The in vitro release study showed satisfactory release of amlodipine besilate from the immediate release layer showed 100.02% release in 60 min.

In vitro dissolution study for metaprolol succinate (SR)

The in vitro drug release profiles of Metaprolol succinate were obtained. The in vitro release study showed satisfactory release of metaprolol succinate from the sustained release layer F7,F8,F9 containing HPMCK100M showed 93.47, 88.12, 85.15% drug release respectively in 20 hours [84-92].

Conclusion

Bilayer tablets of Amlodipine besylate and Metoprolol succinate were prepared by direct compression technique and were found to be good without chipping, capping and sticking. Infrared spectroscopic studies indicated that the drug is compatible with the polymers. The drug content was uniform in all the formulations of prepared tablets. Drug release (Metoprolol succinate) was found to approximately followsfirst order, non-Fickian diffusion. From the reproducible results obtained from the executed experiments it can be concluded that Increase in amount of CCS, in Amlodipine layer increases the release of Amlodipine. ccs 20% is sufficient for complete release of Amlodipine in 45min [93-100]. Increase in the amounts of HPMC K100M and pvpk30 in Metoprolol layer decreases the release of Metoprolol. HPMC K100m (%) and PVPK30 (%) are suitable for sustain release of Metoprolol over a period of 20 hours. On the basis of in-vitro release studies and its kinetic data was selected as optimized formulations for designing Bilayer tablets of Amlodipine besylate and Metoprolol succinate. SBased on mathematical models, it was concluded that formulation F7, F8,and F9 fitted into first order and show non-Fickian diffusion mechanism of Metoprolol release. Short-term stability studies indicated no appreciable changes in the drug content and in vitro drug release rates of formulation. Thus Bilayer drug delivery system can be considered as one of the promising formulation technique.

e-ISSN: 2320-1215
p-ISSN: 2322-0112

REFERENCES

1. Tacyildiz N, Tanyildiz G, Soydal C, Ozkan E, Kucuk O, et al. (2015) Assessment of Sorafenib and AntiVEGF Combination Therapy Response which Added to Neoadjuvant Therapy in two Pediatric Metastatic Ewing Sarcoma Patients by Fluorine-18 Fluorodeoxyglucose Positron Emission Tomography (18F-PET) Method: It may Determine the Prognosis. J Nucl Med Radiat Ther 6: 212.
2. Türker K, Tas B, AltinayS, Tas E (2014) Widespread Dystrophic-Anagen Alopecia and Drug Eruption due to Usage of PEG-IFN α-2a / Ribavirin Combination Therapy. Hair Ther Transplant 4: 129.
3. Mahoney S, Arfuso F, Millward M, Dharmarajan A (2014) The Effects of Combination Treatment Using Phenoxodiol and Docetaxel, and Phenoxodiol and Secreted Frizzled-related Protein 4 on Prostate Cancer Cell Lines. J Carcinog Mutagen 5: 203.
4. Mahara F, Miyamoto K, Fujita H, Mutsuda T (2014) Clinical Usefulness of Combined Therapy Involving Minocycline and Ciprofloxacin as a Treatment for Fulminant Cases of Japanese Spotted Fever. Clin Microbiol 3: 176.
5. Li Y, Dong H, Li X, Shi D, Li Y (2014) Single Polymer-drug Conjugate Carrying Two Drugs for Fixed-dose Co-delivery. Med chem 4: 672-683.
6. Lapchak PA, Boitano PD (2014) Effect of the Pleiotropic Drug CNB-001 on Tissue Plasminogen Activator (tPA) Protease Activity in vitro: Support of Combination Therapy to Treat Acute Ischemic Stroke. J Neurol Neurophysiol 5: 214.
7. Rita K, Satoto TB, Iwan D, Hari K (2014) The Use of Artesunate Combination Therapy (Acts) and Long- Lasting Insecticidal Net (LLIN) in Low Endemic Area to Achieve Malaria Elimination in Indonesia. Malar Chemoth Cont 3: 118.
8. Zhang X, Tang D, Yang J, Shi K, Gao J, et al. (2014) Combination of Sertraline and Sildenafil versus Sertraline Monotherapy in the Treatment of Acquired Premature Ejaculation without Concomitant Diseases. Andrology 3: 117.
9. Shirai T, Kawayama T, Nagase H, Inoue H, Sato S, et al. (2014) Exhaled Nitric Oxide Measurement may Predict Asthma Exacerbation after Stepping down Formoterol/Budesonide Combination Therapy in Adult Asthma. J Allergy Ther 5: 173.
10. Suzuki H, Hoshi H, Inoue T, Kikuta T, Takane H, et al. (2013) Starting with PD Enables Diversity of Later Treatments. J Nephrol Therapeutic S1: 004.
11. Yamamoto Y, Chaki O, Nakayama M (2014) Two Cases of Non- Hodgkinâ€™s Lymphoma Involving the Uterus. Gynecol Obstet (Sunnyvale) 4: 213.
12. Suzuki H, Hoshi H, Inoue T, Kikuta T, Takane H, et al. (2013) Starting with PD Enables Diversity of Later Treatments. J Nephrol Therapeutic S1: 004.
13. Asai N, Ohkuni Y, Kaneko N (2013) A Successful Case of Persistent Asthma in the Treatment of Inhalation Corticosteroid Combination Therapy of Budesonide/Folmoterol and Ciclesonide. J Clin Case Rep 3: 296.
14. Gladue HS, Fox DA, Lowe L, Kahlenberg JM (2014) Schnitzlerâ€™s Syndrome in the Absence of a Monoclonal Gammopathy: A Report of Two Cases. J Clin Cell Immunol 5: 265.
15. Birkenkamp KE, Lauzardo M, Mangura BT, Brito MO, Griffith DE, et al. (2014) Diagnosis and Management of Tuberculosis in Candidates for Tumor Necrosis Factor Alpha Antagonists: An Experts Survey. J Mycobac Dis 4: 171.
16. Kadiri SK, Yarla NS, Vidavalur S (2014) Screening and Isolation of Antagonistic Actinobacteria Associated With Marine Sponges from Indian Coast. J Microb Biochem Technol S8: 003.

17. Ashkenazi J, Bar-Hava I, Meltcer S, Rabinsona J, Anteby EY, et al. (2014) The Role of GnRH-Analogues used in Elderly (>38 yrs) Patients Undergoing Controlled Ovarian Hyperstimulation for IVF. JFIV Reprod Med Genet 2: 128.
18. Donio MBS, Velmurugan S, Raman K, Babu MM, Citarasu T (2014) Antagonistic Bacillus cereus TC-1 Isolated from Solar Salt Work in Southern India. J Microb Biochem Technol 6: 242-246.
19. Chang E, He L (2014) Antagonistic Effects of Insulin Signaling and Glucagon Signaling on Controlling Hepatic Gluconeogenic Gene Expression. Pediat Therapeut 4: 200.
20. Rashmi R Kokardekar, Yogesh S Chaudhari, Suresh D Kumavat, Harshal A Pawar (2014) Clin Pharmacol Biopharm 4: 1.
21. Fentie M, Belete A, Mariam TG (2015) Formulation of Sustained Release Floating Microspheres of Furosemide from Ethylcellulose and Hydroxypropyl Methylcellulose Polymer Blends. J Nanomed Nanotechnol 6: 262.
22. Swed A, Cordonnier T, Fleury F, Boury F (2014) Protein Encapsulation into PLGA Nanoparticles by a Novel Phase Separation Method Using Non-Toxic Solvents. J Nanomed Nanotechnol 5: 241.
23. Damodar R, Movva B (2014) Preparation and In-vitro Evaluation of Metformin HCl Tablets Containing Sustained Release Beads for Increasing Therapeutic Window. J Bioequiv Availab 6: 091-095.
24. Madhavi N, Sudhakar B, Ravikanth PV, Mohon K, Ramana Murthy K (2012) Formulation and Evaluation of Phenytoin Sodium Sustained Release Matrix Tablet. J Bioequiv Availab 4: 128-133.
25. Madhavi N, Sudhakar B, Ravikanth PV, Mohon K, Ramana Murthy K (2012) Formulation and Evaluation of Phenytoin Sodium Sustained Release Matrix Tablet. J Bioequiv Availab 4: 128-133.
26. Babu B, Meyyanathan SN, Gowramma B, Muralidharan S, Elango K, et al. (2012) Pharmacokinetic Evaluation of Newly Developed Oral Immediate Release and Sustained Release Dosage Forms of Losartan Potassium. J Bioequiv Availab 4: 121-127.
27. Yamano S, Lin TY, Dai J, Fabella K, Moursi AM (2011) Bioactive Collagen Membrane as a Carrier for Sustained Release of PDGF. J Tissue Sci Eng 2: 110.
28. Venkatesh DN, Sankar S, Meyyanathan SN, Muralidharan S, Shanmugam R,et al. (2009) Bioavailability Studies on Developed ProchlorperazineMaleate Sustained Release Tablets by HPLC. J Bioanal Biomed 1: 054-057.
29. Marín LE, Carvallo BC, Coca AH, Barragán GB, García OG, et al. (2015) 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 7: 001-004.
30. Khorshid AF (2014) Chemically Modified Carbon Sensors Mixed or Single for the Determination of Cardiovascular Drug Nafronyl Oxalate in Bulk, Praxilene and Human Fluids. J Biosens Bioelectron 5: 153.
31. Enriquez GG, Orawiec BA, Rizvi SAA, Do DP (2014) Formulation Development and In vitro Evaluation of Oral Extended-release Capsules Containing Biodegradable Microspheres. J Nanomed Nanotechnol 5: 208.
32. Tariq MH, Naureen H, Abbas N, Akhlaq M (2015) Development and Validation of a Simple, Accurate and Economical Method for the Analysis of Vancomycin in Human Serum Using Ultracentrifuge Protein Precipitation and UV Spectrophotometer. J Anal Bioanal Tech 6: 239.
33. Naveed S, Shafiq A, Khan M, Jamal M, Zafar H, et al. (2014) Degradation Study of Available Brands of Metformin in Karachi Using UV Spectrophotometer. J Diabetes Metab 5: 328.
34. Naveed S (2013) An Overview of Analytical Determination of Captopril in Active Pharmaceutical Ingredients (API) Formulation and Biological Fluids. J Bioequiv Availab 5: 264-266.

35. Jain R, Sahu V, Jain N, Jain S (2011) Mixed Hydrotropy Solubilization Approach for Quantitative Estimation of Eprosartan Mesylate and Hydrochlorthiazide by UV Spectrophotometer. Pharm Anal Acta 2: 135.
36. Agrawal P (2015) Significance of Polymers in Drug Delivery System. J Pharmacovigil 3:e127.
37. Gavasane AJ, Pawar HA (2014) Synthetic Biodegradable Polymers Used in Controlled Drug Delivery System: An Overview. Clin Pharmacol Biopharm 3: 121.
38. Kolitz-Domb M, Margel S (2014) Engineered Narrow Size Distribution High Molecular Weight Proteinoids, Proteinoid-Poly(L-Lactic Acid) Copolymers and Nano/Micro-Hollow Particles for Biomedical Applications. J Nanomed Nanotechnol 5: 216.
39. Chlupac J, Filova E, Riedel T, Brynda E, Pamula E, et al. (2014) Endothelial Cell Lining of PET Vascular Prostheses: Modification with Degradable Polyester-based Copolymers and Adhesive Protein Multi-layers. J Tissue Sci Eng 5: 139.
40. Shirmanova MV, Gavrina AI, Aksenova NA, Glagolev NN, Solovieva AB,et al. (2014) Comparative Study of Tissue Distribution of Chlorin e6 Complexes with Amphiphilic Polymers in Mice with Cervical Carcinoma. J Anal Bioanal Tech S1: 008.
41. Chandra VV, Deepthi T, Sashikanth S, Lavanya Y, Damodar R (2014) Analysis of Sustained Unleash Indefinite Quantity Type of Anti-Diabetic Coordination of Deliquescent Polymers. J Mol Pharm Org Process Res 2: R1-002.
42. Gleadall A, Pan J (2013) Computer Simulation of Polymer Chain Scission in Biodegradable Polymers. J Biotechnol Biomater 3: 154.
43. Matsuda T, Shirota T, Kawahara D (2014) Fabrication Factory for Tubular Vascular Tissue Mimics based on Automated Rolling Manipulation and Thermo-Responsive Polymers. J Tissue Sci Eng 5: 134.
44. Vidyasagar A (2013) Stimuli Responsive Polymers for Biophysical Applications. J Phys Chem Biophys 3: e116.
45. Suedee R (2013) The Use of Molecularly Imprinted Polymers for Dermal Drug Delivery. Pharm Anal Acta 4: 264.
46. Yuen John WM, Yung Jolene YK (2013) Medical Implications of Antimicrobial Coating Polymers-Organosilicon Quaternary Ammonium Chloride. Mod Chem appl 1: 107.
47. Rohini, Neeraj A, Anupam J, Alok M (2013) Polymeric Prodrugs: Recent Achievements and General Strategies. J Antivir Antiretrovir S15.
48. Jian PU, Fukushi K (2013) Phytoextraction of Cadmium from Contaminated Soil Assisted By Microbial Biopolymers. Agrotechnol 2: 110.
49. Wettig SD, Kamel AO (2013) Thermodynamic Studies of DNA-Cationic Components Interactions Using Titration Calorimetry. J Thermodyn Catal 4: 121.
50. Haik Y (2012) Ionic Liquid Mediated Conductive Polymers. J Appl Mech Eng 2: e112.
51. Chauhan A (2012) Polymers and its Modifications. Pharmaceut Anal Acta 3: e128.
52. Patel Manish P, Patel Jayvadan K, Patel Ravi R, Patel Kalpesh N (2012) Microencapsulation of Verapamil Hydrochloride: A Novel Approach for Gastric Retention Using Different Polymers. Med chem 2: 076-080.
53. Kuhn-Thiel AM, Wehling M (2014) Antihypertensive Drugs in the Elderly: Risks and Benefits as Evaluated by the FORTA Method. J Gerontol Geriatr Res 3: 1000171.
54. García AR, Fonte M, Erroz IO, Vázquez JAI, Vázquez LS, et al. (2014) Recognition and Initial Treatment of Suspected Intracranial Hypertension by Primary Care Pediatricians: An Advanced Simulation Observational Study. Emerg Med (Los Angel) 4: 205.
55. Ishikawa Y (2014) Obstructive Sleep Apnea and Hypertension; A New Way to Go. J Sleep Disorders Ther 3: e128.

56. Sang LY, Liang YX, So KF, Leung GK, Ellis-Behnke RG, et al. (2014) A Self-assembling Nanomaterial Reduces Acute Brain Injury and Enhances Functional Recovery in a Rat Model of Hypertensive Intracerebral Hemorrhage. J Nanomed Nanotechnol 5: 224.
57. Tyson CC, Kuchibhatla M, Patel UD, Pun PH, Chang A, et al. (2014) Impact of Kidney Function on Effects of the Dietary Approaches to Stop Hypertension (Dash) Diet. J Hypertens 3: 168.
58. Hu SS, Zhang HG, Zhang QJ, Xiu RJ (2014) Increased Circulating Apoptotic CD31+/CD42b- and Activated CD62E+ Endothelial Micro Particles in Coronary Artery Disease. J Hypertens 3: 167.
59. Kossaify A, Karam M (2014) Markers in Hypertension: Insights for an Enhanced Blood Pressure Management. J Hypertens 3: 165.
60. karter Y (2014) Oxidative Stress and Endothelial Dysfunction in White Coat Hypertension: Data of the Group from Cerrahpasa Medical Faculty. J Hypertens 3: 163.
61. Liu Z, Wu J, Zhang J, Liu Y, Liu B, et al. (2014) The Association Study of PRKG1 Gene Polymorphism and Salt-Sensitive Hypertension among the Essential Hypertension in Beijing. J Hypertens 3: 162.
62. Ding X, Yang Z, Han Y, Yu H (2014) Mitochondrial Long Chain Fatty Acid Oxidation Related Enzyme Changes in Different Preeclampsia- Like Mouse Models. J Hypertens 3: 161.
63. Wei G, Jansen SA, Williamson S, Brown M (2014) Assay Profiles of Prostanoids and Female Sex Hormones for Studying Potential Biomarkers of Hypertension. J Hypertens 3: 159.
64. Parlak A, Aydogan U, Mutlu S, Cayci T, Koc B, et al. (2014) Investigation of Pentraxin 3 Levels in Hypertensive Patients with Stroke, Retinopathy and Nephropathy. J Hypertens 3: 158.
65. Skultetyova D, Filipova S, Chnupa P, Madaric J, Fridrich V, et al. (2014) The Impact of Blood Pressure on Carotid Artery Stiffness and Wave Intensity in Patients with Resistant Hypertension after Renal Sympathetic Denervation. J Hypertens 3: 157.
66. Shukla AN, Madan T, Thakkar BM, Parmar M, Shah K (2014) The Prevalence of Hypertension: Role of Hereditary in Young and Obesity in all. J Hypertens 3: 156.
67. Tibaldi M, Brescianini A, Sciarrillo I, Massaia M, Bo M (2014) Prevalence and Clinical Implications of Orthostatic Hypotension in Elderly Inpatients. J Hypertens 3: 155.
68. Hoshida S, Nakagawa T, Shinoda Y, Inui H, Watanabe T (2014) Analysis of the Difference in the Pressure-Natriuresis Relationship Based on the Class of Medication Using Spot Urine Tests in Hypertensive Patients. J Hypertens 3: 154.
69. Dutta AK, Ikiki E (2013) Novel Drug Delivery Systems to Improve Bioavailability of Curcumin. J Bioequiv Availab 6: 001-009.
70. Vijaya Shanti B, Mrudula T, Pavan Kumar V (2011) An Imperative Note on Novel Drug Delivery Systems. J Nanomedic Nanotechnol 2: 125.
71. Chang E, McClellan AJ, Farley WJ, Li DQ, Pflugfelder SC, et al. (2011) Biodegradable PLGA-Based Drug Delivery Systems for Modulating Ocular Surface Disease under Experimental Murine Dry Eye. J Clinic Experiment Ophthalmol 2: 191.
72. Khan DR (2010) The use of Nanocarriers for Drug Delivery in Cancer Therapy. J Cancer Sci Ther 2: 058-062.
73. Kadiri SK, Yarla NS, Vidavalur S (2014) Screening and Isolation of Antagonistic Actinobacteria Associated With Marine Sponges from Indian Coast. J Microb Biochem Technol S8: 003.
74. Abdelmeged A, Abdalah A, Mahran A, Gamal A, Elgendy E (2015) A Comparative Study between GnRH Antagonist and Long Agonist Protocols in Patients with Polycystic Ovarian Syndrome (PCOS) Undergoing in vitro Fertilization. JFIV Reprod Med Genet 3: 137.
75. Werner FM, Covenas R (2014) Might Combined GABAA Agonists and NMDA Antagonists have a Therapeutic and maybe a Prophylactic Effect in Alzheimer's and Parkinson's Disease?. J Cytol Histol 6: 298.

76. McLaughlin and Ian SZagon (2014) Opioid Antagonists Enhance Diabetic Wound Closure: A New Therapy. Transl Med (Sunnyvale) 4: 142.
77. Gladue HS, Fox DA, Lowe L, Kahlenberg JM (2014) Schnitzlerâ€™s Syndrome in the Absence of a Monoclonal Gammopathy: A Report of Two Cases. J Clin Cell Immunol 5: 265.
78. Birkenkamp KE, Lauzardo M, Mangura BT, Brito MO, Griffith DE, et al. (2014) Diagnosis and Management of Tuberculosis in Candidates for Tumor Necrosis Factor Alpha Antagonists: An Experts Survey. J Mycobac Dis 4: 171.
79. Simone TM, Higgins SP, Higgins CE, Lennartz MR, Higgins PJ (2014) Chemical Antagonists of Plasminogen Activator Inhibitor-1: Mechanisms of Action and Therapeutic Potential in Vascular Disease. J Mol Genet Med 8: 125.
80. Kadiri SK, Yarla NS, Vidavalur S (2014) Screening and Isolation of Antagonistic Actinobacteria Associated With Marine Sponges from Indian Coast. J Microb Biochem Technol S8: 003.
81. Sabouret P, Sartral MT, Kevorkian JP, Verges B (2014) Antiplatelet Agents in Diabetic Patients: Clinical Advances and Remaining Questions. J Clin Exp Cardiolog 5: 330.
82. Arayne SM, Sultana N, Shehnaz H, Haider A (2014) Synthesis and Characterization of α,α-Dimethyl-4-[1-Hydroxy-4-[4-(Hydroxyldiphenyl- Methyl)-1-Piperidinyl]Butyl] Benzeneacetic Acid Metal Complexes of Biological Interest. Mod Chem appl 2: 127.
83. Donio MBS, Velmurugan S, Raman K, Babu MM, Citarasu T (2014) Antagonistic Bacillus cereus TC-1 Isolated from Solar Salt Work in Southern India. J Microb Biochem Technol 6: 242-246.
84. Bendtsen M, Zou X, Jørgensen HS, Bünger CE (2014) An Anti TNF-A Receptor Antagonist does not Augment the Effect of Autologous Mesenchymal Stem Cell Therapy in Experimental Intervertebral Disc Degeneration in Göttingen Minipigs. J Stem Cell Res Ther 4: 187.
85. Källén B (2014) Maternal Asthma and Use of Antiasthmatic Drugs in Early Pregnancy and Congenital Malformations in the Offspring. J Pulm Respir Med 4: 166.
86. Rehman HU (2013) Paradoxical Increased Risk of Thrombosis after Initiation of Vitamin K Antagonists in Thromboembolic Disease. J Clin Case Rep 3: e121.
87. Heifetz A, Mazanetz MP, James T, Pal S, Law RJ, et al. (2013) From Receptors to Ligands: Fragment-assisted Drug Design for GPCRs Applied to the Discovery of H3 and H4 Receptor Antagonists. Med chem 4: 313-321.
88. Zhao J, Ye Q, Wan Q, Zhou J (2013) Analysis of TNF-ÃŸ, IL-10, and IL-1 Cluster Gene Polymorphisms and Clinical Risk Factors on Acute Renal Graft Rejection. Intern Med 3: 129.
89. Masayuki O, Matsuse H, Takano Y, Yamada S, Ohshima H, et al. (2013) Oxygen Uptake during Aerobic Cycling Exercise Simultaneously Combined with Neuromuscular Electrical Stimulation of Antagonists. J Nov Physiother 3: 185.
90. Nascimento J, Antunes H (2013) Inflammatory Bowel Disease-Experience of a Pediatric Gastroenterology Unit. Pediat Therapeut 3: 173.
91. Vuoristo-Mylys S, Laaksonen E, Lahti J, Lipsanen J, Alho H, Kalska, H. et al. (2013) Predictors of Self-Reported Adherence to Naltrexone Medication in an Outpatient Treatment for Problem Drinking. J Addict Res Ther 4: 159.
92. Mohsen IA, Youssef MAFM, Elashmwi H, Darwish A, Mohesen MN, et al. (2013) Clomiphene Citrate plus Modified GnRH Antagonist Protocol for Women with Poor Ovarian Response Undergoing ICSI Treatment Cycles: Randomized Controlled Trial. Gynecol Obstet 3: 158.
93. Barton JC, Adams PC, Acton RT, Speechley M, McLaren CE, et al. (2013) Proton Pump Inhibitors and Lower Serum Ferritin Levels in 171 HFE C282Y Homozygotes in the Hemochromatosis and Iron Overload Screening Study. Vitam Miner 2: 112.
94. Moore T, Globa L, Barbaree J, Vodyanoy V, Sorokulova I (2013) Antagonistic Activity of Bacillus Bacteria against Food-Borne Pathogens. J Prob Health 1: 110.

95. Omotuyi O, Ueda H (2013) Descriptor-based Fitting of Structurally Diverse LPA1 Inhibitors into a Single predictive Mathematical Model. J Phys Chem Biophys 3: 121.
96. Brierley GV, Fung KYC, Purins L, Priebe IK, Tabor B, et al. (2013) Circulating Levels of the Wnt Antagonist Dkk-3 as a Diagnostic Marker for Colorectal Cancer. J Mol Biomarkers Diagn S8: 008.
97. Akhtyamova N, Sattarova RK (2013) Endophytic Yeast Rhodotorula rubra Strain TG-1: Antagonistic and Plant Protection Activities. Biochem Physiol 2: 104.
98. Rajput H (2013) Effects of Atropa belladonna as an Anti-Cholinergic. Nat Prod Chem Res 1: 104.
99. Hanefeld M, Schell E, Gouni-Berthold I, Melichar M, Vesela I, et al. (2012) Orally-Administered Chemokine Receptor CCR2 Antagonist CCX140-B in Type 2 Diabetes: A Pilot Double-Blind, Randomized Clinical Trial. J Diabetes Metab 3: 225.
100. Gillespie C, Quarshie A, Penichet M, Gonzalez-Perez RR (2012) Potential Role of Leptin Signaling in DMBA-induced Mammary Tumors by Non- Responsive C57BL/6J Mice Fed a High-Fat Diet. J Carcinogene Mutagene 3: 132.