Research Article

Available Online at: www.ijpir.com

International Journal of Pharmacy and Industrial Research

ISSN Print 2231 – 3648
Online 2231 – 3656

Formulation of tizanidine hydrochloride loaded solid-lipid nanoparticles using emulsification-solvent diffusion technique

Preethi Fernandiz[1], Suresh N[2]*, Kerryn Joseph A D'Silva[3], Ravi KV[2]

[1]Department of Pharmacy Practice, D.R.Karigowda College of Pharmacy, Hassan, Karnataka – 573201, India.
[2]Department of Pharmaceutics, D.R.Karigowda College of Pharmacy, Hassan, Karnataka – 573201, India
[3]Department of Pharmaceutical Chemistry, D.R.Karigowda College of Pharmacy, Hassan, Karnataka – 573201, India

ABSTRACT

The present study aimed to formulate Tizanidine HCl loaded solid lipid nanoparticles for improved drug delivery. Tizanidine hydrochloride is a centrally acting α2-receptor agonist which regulates myotonolytic effects on skeletal muscle. Tizanidine Hydrochloride is a muscle relaxant drug used to treat muscle spasms. Tizanidine HCl-loaded SLNs were prepared by the emulsification-solvent diffusion method using different ratio of lipid materials (Glycerol monostearate & stearic acid) and non-ionic surfactants. Twelve batcheswere prepared using different excipients and the formulations were physiochemically stable throughout the study period. Finally, Tizanidine HCl loaded solid lipid nanoparticles decreases the number of application of drugs.

Keywords: Tizanidine HCl, Muscle spasm, Solid lipid nanoparticles, Non-ionic surfactants and lipids

INTRODUCTION

Nanoparticles are used as a substitute for conventional emulsions, polymeric nanoparticles and liposomes as drug carriers. The successful application of nanoparticles in drug delivery depends upon its penetration through anatomical barriers, sustained-release effect and stability in nanometric size. The use of nanoparticles in clinical medicine is limited due to the scarcity and high cost of safe, regulatory-approved polymers[1]. As an alternative carrier, lipids have been put forward in lipophilic pharmaceuticals to address the shortcomings of traditional carriers.Such lipid nanoparticles are referred to as solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs), which attract the worldwide attention of formulators[2].

Tizanidine hydrochloride is a centrally acting α2-receptor agonist which regulates myotonolytic effects on skeletal muscle. Tizanidine Hydrochloride is a muscle relaxant drug used to treat muscle spasms. It exhibits a short half-life of 2.5-3 hours, a low bioavailability of around 21-40%. Reduced bioavailability may cause a decrease in its effectiveness. The normal dosage of Tizanidine hydrochloride is approximately 2-4 mg twice a day, which can be increased within 24 hours to a maximum of 36 mg.Tizanidine undergoes extensive first-pass metabolism, which contributes to imidazole ring breakdown and aromatic ring and sulphur atom oxidation. Hence, these characteristics make Tizanidine hydrochloride as a suitable candidate for the formulation of solid lipid nanoparticles[3].

The main objective of the present investigation was to prepare solid lipid nanoparticles incorporated Tizanidine Hydrochloride by emulsification-solvent diffusion method.

Experimental methods

Melting Point

The melting point of the drug was determined by using a melting point apparatus (Thiele's tube). Thiswas compared with the literature melting point value of the drug. The melting point of the pure drug Tizanidine HCl was found to be at 280 ±0.5ºC.

Author for Correspondence:
Suresh N,
Department of Pharmaceutics, D.R. Karigowda College of Pharmacy, Hassan, Karnataka – 573201, India.

Preparation of phosphate buffer

Take accurate amount i.e. 27.2 gm of potassium dihydrogen orthophosphate (KH_2PO_4) and dissolved in1000mL water. And 8 gm sodium hydroxide pellets were dissolved in 1000 mL of the beaker. 180 mL of this prepared sodium hydroxide solution and about 250mL of the prepared potassium dihydrogen orthophosphate solution was added into 1000mL measuring cylinder and the volume is made up to 900mlusing water. The pH is adjusted using NaOH or dilute HCl solution[4].

Determination of λmax

100 mg of Tizanidine HCl was accurately weighed and dissolved in 100 ml of methanol in a volumetric flask. 10 ml of the above solution was diluted with 100 ml of methanol (=10 µg/mL) ina separate volumetric flask and scanned for maximum absorbance in UV double beam spectrophotometer (Shimadzu 1800) in the range from 200 to 400 nm, using methanol as blank. The λmax of the drug was found to be 228nm[5].

Standard Curve forTizanidine HCl

100 mg of Tizanidine HCl was accurately weighed and dissolved 50 ml of methanol. The solution was sonicated for 10 min and the final volume was adjusted to 100mL to give stock solution-I (1000 µg/mL concentration). 10 mL of stock solution-I was placed in 100 mL volumetric flask and volume were adjusted with methanolto give stock solution-II of 100µg/mL concentration. Stock solution-II was further diluted with methanol to get working standard solution of 4, 8, 12, 16, 20, 24, µg/mL of Tizanidine HCl to construct Beer's law plotfor the pure drug. The absorbance of the solutions was measured at 228 nm using UV-visiblespectrophotometer. A graph of concentration Vs absorbance was plotted[5].

Compatibility study using FT-IR

Using a Thermo Nicolet FTIR, infrared spectroscopy was performed and the spectrum was registered in the 4000 to 400 cm^{-1} region. The treatment consisted of sample dispersion (drug and drug-excipient combination, 1:1 ratio) in KBr (200-400 mg) and compression into discs by applying a hydraulic pressing pressure of 5 tonnes for 5 minutes. All spectra at a resolution of 2 cm^{-1} were gathered as an average of three scans.The interaction between drug-excipients was observed from IR□Spectral studies by observing any shift in peaks of the drug in the spectrum of a physical mixture of the drug[6].

Preparation of Solid lipid Nano-particles with Tizanidine HCl

Tizanidine HCl-loaded SLNs were prepared by the emulsification-solvent diffusion method. Briefly, a fixed amount of Tizanidine HCl (4 mg) and different quantities of lipid materials (Glycerol monostearate & stearic acid) were dissolved in 2 mL acetone/ethanol mixture at various proportions. The aqueous phase contained a different concentration of surfactant (tween 80, span 20 and poloxamer 188) in different volumes. Both phases were pre-heated to 40°C and then the organic phase was dripped into the aqueous phase with a syringe. The mixture was stirred for 30 min to remove acetone and ethanol. The suspension was then sonicated for 30 minutes using a probe sonicator set at 50 W energy output during various times to obtain Tizanidine HCl loaded SLNs[7].

RESULTS AND DISCUSSION

Tizanidine HCl is an alpha2-adrenergic agonist with a chemical structure unrelated to other muscle relaxants and a centrally active myotonolytic skeletal muscle relaxant.About 53% to 66% of the dose administered is being absorbed through the gastrointestinal tract after oral administration and the peak plasma concentration is reached within 1 to 2 hours. Bioavailability of Tizanidine is about 34% to 40% and the half-life is 2.5 hours. Hence, this study aims to formulate SLNs loaded Tizanidine. Tizanidine-loaded SLNs were prepared by the emulsification-solvent diffusion method using different quantities of lipids i.e. Glycerol monostearate (GMS) & stearic acid. Tween 80, span 20 and Poloxamer 188 were used as non-ionic surfactants. Tweens and spans are the popular non-ionic surfactants used as vesicles forming agent in the preparation of SLNs their effect on the drug entrapment, vesicle size and drug release profile were determined. A total of 12batches of SLNs were prepared using the varying ratio of GMS and steric acid and non-ionic surfactants.

Pre-formulation studies

Melting point determination

The measurement of melting point is a measure of concern in pharmaceutical studies. The most important reason to determine the melting point during pre-formulation is crystalline solubility such studies are particularly important because the scarcity of available drug powder often precludes accurate solubility determinations. Melting point and solubility are related via the latent heat of fusion, which is the amount of heat generated during melting or fusion. In the present work,the melting point was determined by the capillary tube method. The melting point of pure drug Tizanidine HCl was found to be 280±0.5ºC, which is identical to the melting point reported by the Drug Bank database. In this temperature range, the solid structure is transformed into a stable liquid without altering the chemical entity of the substance. Hence, the obtained result confirms the purity of the drug.

Analytical method determination of Tizanidine HCl

The technique of ultra-violet spectrophotometry is one of the most frequently employed in pharmaceutical analysis. It involves the measurement of the amount of the ultraviolet (190-380nm) or visible (380-800 nm) radiation absorbed by a substance in solution.

Determination of λmax

UV method was used to determine the λmaxof pure drug. Tizanidine HCl. The λmax of the Tizanidine HCl was found to be 228 nm in methanol and the same wavelength was used for further studies. The UV spectrum of Tizanidine HCl is shown in figure 1.

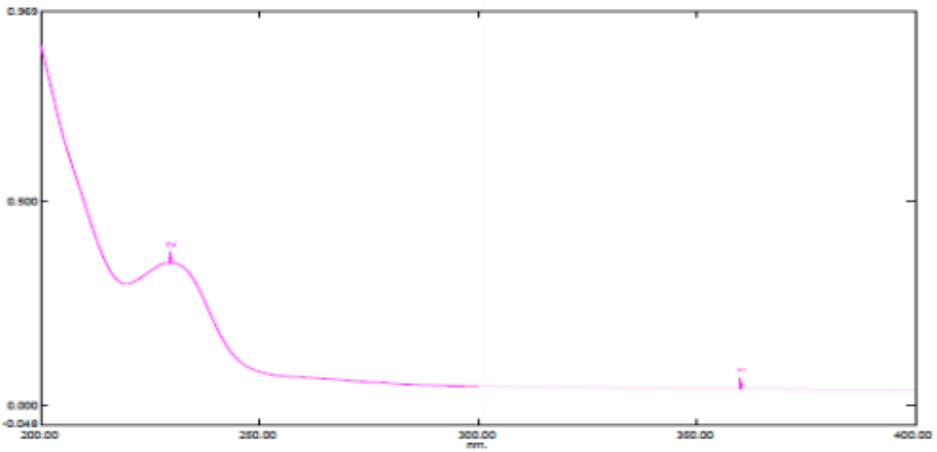

Figure 1: UV spectrum of Tizanidine HCl in distilled water

Determination of the calibration curve

The calibration curve of Tizanidine HCl was determined by UV spectrophotometer at 228 nm using methanol as a blank. Tizanidine HCl pure drug obeyed Beer-Lambert's law in the range of 4-24µg/ml. The calibration curve was obtained by plotting the absorbance against drug concentrations (figure 1 and table 1). The data were analysed in MS-Excel-2007. The correlation coefficient (r2) was found to be 0.999 in methanol which indicates the linearity.

Table 1: Spectrophotometric data of Tizanidine HCl

Sl. no	Concentration (µg/ml)	Absorbance at 228nm			Average	Std. Dev (±)
		Trial 1	Trial 2	Trial 3		
1.	4	0.113	0.123	0.112	0.116	0.0240
2.	8	0.264	0.270	0.258	0.267	0.0281
3.	12	0.398	0.399	0.440	0.412	0.0237
4.	16	0.585	0.580	0.593	0.586	0.0395
5.	20	0.767	0.724	0.710	0.725	0.0270
6.	24	0.912	0.903	0.908	0.909	0.0483

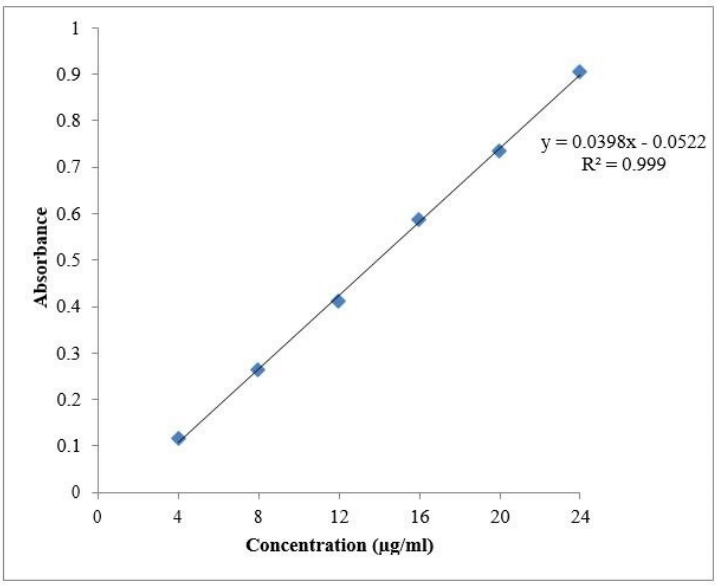

Figure 2: Calibration curve of Tizanidine HCl in methanol

Drug Excipients Interaction Study

While designing any drug delivery system, it is imperative to consider thecompatibility of drug and polymer used within the system. Therefore, it is necessary toconfirm that the drug is not interacting with the polymer under experimental conditions and shelflife. The interaction studies can be done based on Assay, UV, Infra-red and TLCanalysis. In this study drug, excipients interaction study was done by FTIR study.

Compatibility studies using FTIR

Infra-red spectrum of drug and polymers were recorded over the KBr disc method and obtainedspectra were shown in figure 3-7 and table 2. The study of the FTIR spectra of Tizanidine HCldemonstrated that the characteristic absorption peaks for -C-H(str) at 3193.87cm^{-1}, CH(bending) at 723.44cm^{-1}, C-C(str) at 1492.20cm^{-1}, C-N (sharp) at 1631.94cm^{-1}, Ar-NH-R at1397.07 cm^{-1}and C-N (str) at 917.33cm^{-1}. This further confirms the purity of Tizanidine HCl.All the characteristic peaks of Tizanidine HCl were present in the spectrum of drug andexcipients mixture, indicating compatibility between drug and excipients. The spectrumconfirmed that there is no significant change in the chemical integrity of the drug. There is nochange in functional group peaks of Tizanidine HCl in all IR spectrum.

Table 2: Results of the FTIR spectrum ofTizanidine HCl

Functional group	Observed peaks cm^{-1}				
	Tizanidine HCl	Drugand Tween80	Drug and Span 20	Drug and Poloxamer 188	Drug mixtures
-C-H(str)	3193.87	3195.66	3195.35	3196.95	3196.19
C-H(bend)	723.44	725.35	723.83	732.91	723.52
C-C(str)	1492.20	1491.32	1455.25	1491.35	1455.33
C-N (sharp)	1631.94	1634.47	1631.85	1608.06	1633.57
Ar-NH-R	1370.07	1396.93	1397.10	1396.95	1397.10
C-N (str)	917.33	917.32	917.42	917.28	917.20

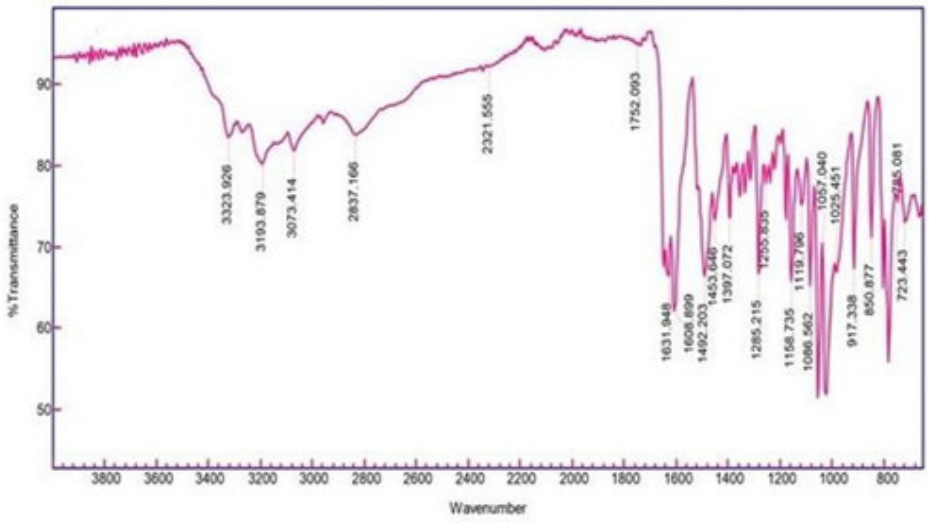

Figure 3: Infrared spectrum of Tizanidine HCl

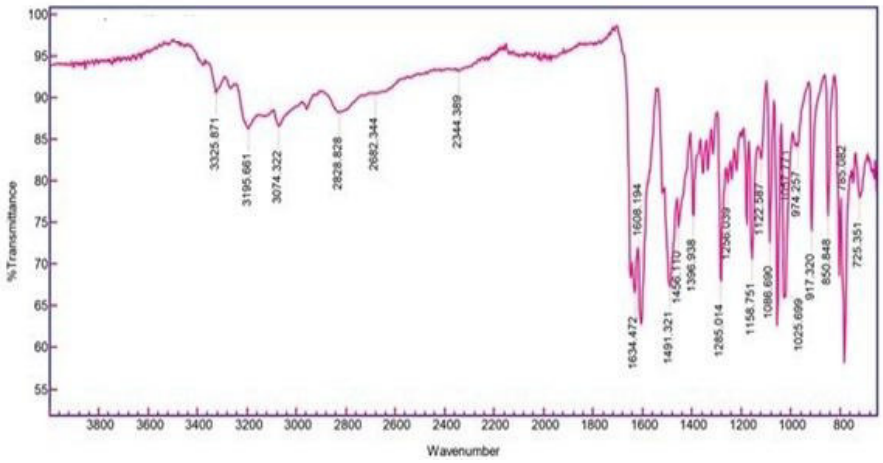

Figure 4: Infrared spectrum of drug and Tween 80

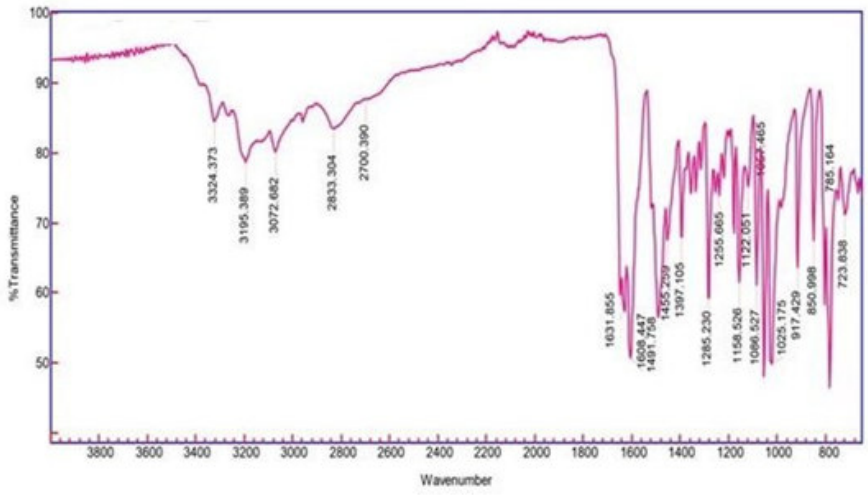

Figure 5:Infrared spectrum of drug and span 20

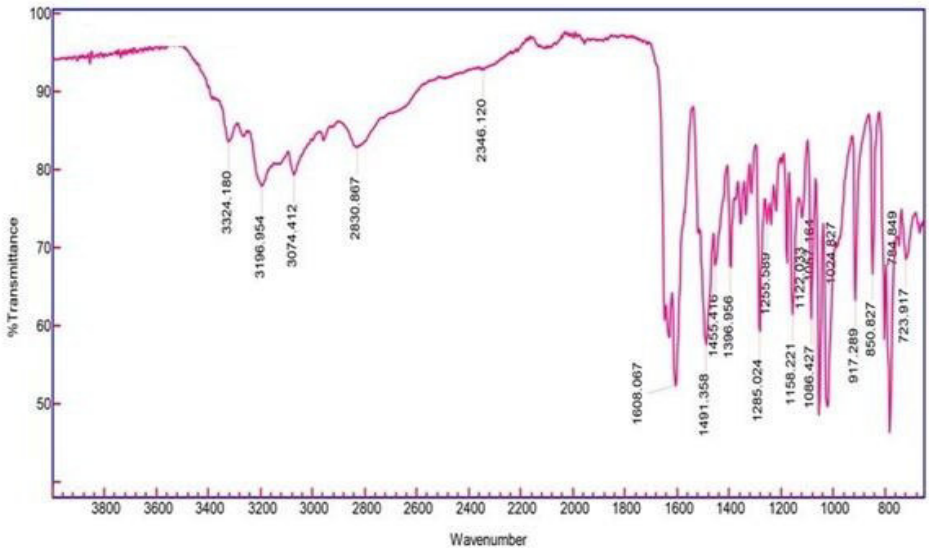

Figure 6:Infrared spectrum of drug and Poloxamer 188

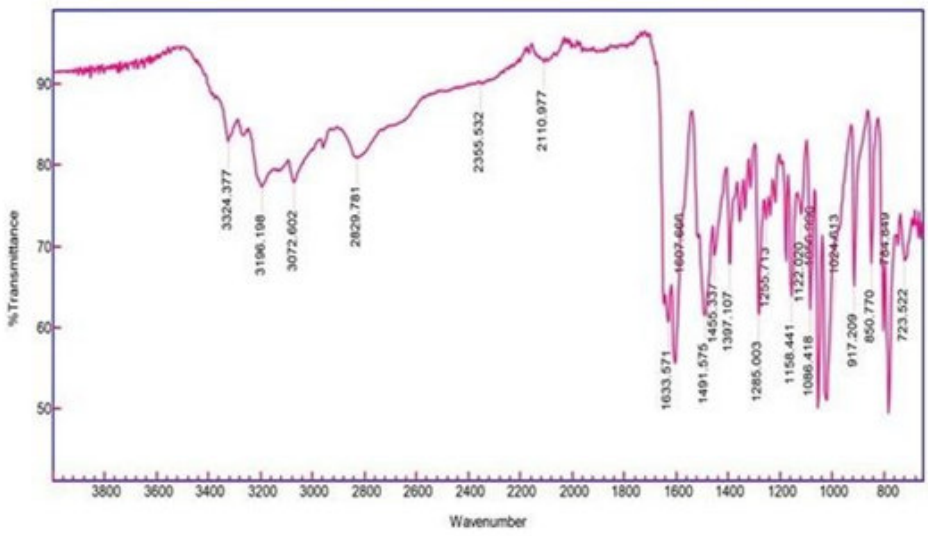

Figure 7: Infrared spectrum of drug and physical mixtures

CONCLUSION

Tizanidine hydrochloride-loaded SLNs were prepared by the emulsification-solvent diffusion method using different ratio of lipids i.e. Glycerol monostearate (GMS) & stearic acid. Tween 80 and span 20 were used as non-ionic surfactants. Tweens and spans are the popular non-ionic surfactants used as vesicles forming agent in the preparation of SLNs their effect on the drug entrapment, vesicle size and drug release profile were determined. A total of 12 batches of SLNs were prepared using the varying ratio of GMS and steric acid and non-ionic surfactants.FT-IR study was carried out to check any possible interactions between the drug and excipients. The pure drug was mixed with 1:1 ratio of excipients and checked for interaction if any. The major FT-IR peaks of the drug were retained in the FTIR physical mixtures. The study results revealed that no major interaction between the selected drug and excipients.

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest involves in the present study.

REFERENCES

1. Rizvi SAA, SalehAM. Applications of nanoparticle systems in drug delivery technology. *Saudi Pharm J*. 2018;26(1):64-70.
2. Talegaonkar S, Bhattacharyya A. Potential of lipid nanoparticles (SLNs and NLCs) in enhancing oral bioavailability of drugs with poor intestinal permeability. *AAPS Pharm Sci Tech.* 2019;20(3):121-9.
3. Xing XW, Sun YF, Zhao J, Pan ZX, Jiang WX. Tizanidine hydrochloride exhibits a cytotoxic effect on osteosarcoma cells through the PI3K/AKT signaling pathway. *J Int Med Res.* 2019;47(8):3792□8.
4. Nagadevi B, Kumar KS, Venkanna P, Prabhakar D. Formulation and characterization of tizanidine hydrochloride loaded ethosomes patch. *Int J Pharm Pharma Sci.* 2014;6(4): 199-205.
5. Ekambaram P, Abdul HS. Formulation and evaluation of solid lipid nanoparticles of ramipril. *J Young Pharm.* 2011;3(3):216-20.
6. Nandini PT, Doijad RC, Shivakumar HN, Dandagi PM. Formulation and evaluation of gemcitabine-loaded solid lipid nanoparticles. *Drug Deliv.* 2015;22(5):647-51.
7. Kushwaha AK, Vuddanda PR, Karunanidhi P, Singh SK, Singh S. Development and evaluation of solid lipid nanoparticles of raloxifene hydrochloride for enhanced bioavailability. *Bio Med Res Int.* 2013;1-9.