ORIGINAL ARTICLE

Formulation and Evaluation of Sustained Release Bilayer Tablets of Losartan Potassium

A. Lakshmana Rao[1], Tera Sandhya[2], Pasumarthy Sree Mahalakshmi[2], Kavilikatta Monika Raasi[3], Savala Jyosthna Sri Lakshmi Durga[3], Nayudu Teja[4], Chinthada Joshi[5], Tirumala Setti Jaswitha[4]

[1]Department of Pharmaceutical Analysis, V. V. Institute of Pharmaceutical Sciences, Gudlavalleru, Andhra Pradesh, India, [2]Department of Pharmacology, Institute of Pharmaceutical Technology, Sri Padmavathi Mahila University, Tirupathi, Andhra Pradesh, India, [3]Department of Pharmaceutical Analysis, Nirmala College of Pharmacy, Mangalagiri, Andhra Pradesh, India, [4]Department of Pharmaceutics, V. V. Institute of Pharmaceutical Sciences, Gudlavalleru, Andhra Pradesh, India, [5]Department of Pharmacology and Toxicology, NIPER Mohali, Punjab, India

Abstract

Introduction: Heart disease is very common cause of deaths in the world. Hypertension is the most prevalent form of heart disease. Losartan has wonderful clinical effectiveness in the treatment of essential hypertension and congestive heart failure. Single dose of losartan can maintain the lowering of blood pressure up to 6–8 h. Hence, repetitive medication is required in a day to maintain the blood pressure. Hence, the aim of this work is to formulation and evaluate of sustained release (SR) bilayer tablet of losartan potassium in which the immediate release layer will release the drug within 10 min and SR layer will maintain uniform drug levels over a sustained period of time. **Materials and Methods:** This research work is performed for the partial fulfillment of the degree of master of pharmacy. The tablets were evaluated to thickness, hardness, diameter, weight variation, drug content uniformity, friability, and *in vitro* drug release studies. *In vitro* drug release studies were performed using USP type II apparatus (paddle method) at 50 rpm in 900 ml of 0.1N HCl as dissolution medium for first 2 h and later replacing it with 900 ml pH 6.8 phosphate buffer solution for the remaining time period at 37±0.5°C. **Results:** The results of Fourier transform infrared and differential scanning calorimetry analysis showed that there was no physical and chemical interaction between drug and other excipients. The stability studies of optimized formulation ME5 at 400C/75%RH for 3 months did not show any variation in the tasted parameter and release.

Key words: Bilayer tablets, Drugs, Losartan potassium

INTRODUCTION

Oral drug delivery has been known for decades as the most widely utilized route of administration among all the routes that have been explored for the systemic delivery of drugs. The goal of any drug delivery system is to provide a therapeutic amount of the drug at the site an effective throughout the entire duration of therapy and then maintain the desired drug concentration.[1] Conventional dosage form produces wide range of fluctuation in drug concentration in the blood stream and tissues which leads to reduction or loss in drug effectiveness or increased incidence of side effects with subsequent undesirable toxicity and poor efficiency. However, sustained or controlled drug delivery systems can decrease the frequency of the dosing and also increases effectiveness of the drug by localization at the site of action, reducing the dose required and providing uniform drug delivery.[2]

Different approaches have been proposed to formulate sustained release (SR) tablets for retaining dosage form

Address for correspondence:
Tera Sandhya, Department of Pharmacology, Institute of Pharmaceutical Technology, Sri Padmavathi Mahila University, Tirupathi, Andhra Pradesh, India.
E-mail: sandhyatera99@gmail.com

Received: 21-04-2021
Revised: 22-06-2021
Accepted: 30-06-2021

in stomach. These include bioadhesive or mucoadhesive systems,[3] swelling and expanding systems,[4,5] floating systems,[6,7] and other delayed gastric emptying devices. In recent years, a growing interest has developed in designing drug delivery systems that include an immediate release (IR) component to extended release (ER) dosages.[8-13] To fulfill the specific therapeutic needs of the different diseases, new drug delivery devices are required for a more accurate time-programmed administration of the active ingredients.

On the basis of these considerations, a new oral delivery device was proposed, in the form of a tablet, one portion is formulated to obtain a prompt release of the double-component drug with the aim of reaching a high serum concentration in a short period of time. The second portion is a prolonged release layer which is designed to maintain an effective drug release for a prolonged period of time. The pharmacokinetic advantage relies on the plasma level for fact that drug release from fast releasing component leads to a sudden rise in the blood concentration. However, the blood level is maintained at steady state as the drug is released from the sustaining layer.

Bilayer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances and also for SR tablet in which one layer is IR as initial dose and second layer is maintenance dose. There are various applications of the bi-layer tablet consists of monolithic partially coated or multilayered matrices.

SCHEMATIC PRESENTATION FOR COMPRESSION OF BI-LAYER TABLET

Drug release mechanism

Need of developing bi-layer tablets[14-16]

For the supervision of fixed dose combinations of drugs, prolong the drug product life cycle, manufacture novel drug delivery systems such as floating or mucoadhesive bilayer tablets for gastroretentive drug delivery systems.

Advantages of bi-layer tablets[17,18]

1. Bi-layer execution with optional single layer conversion kit
2. Low cost compared to other dosage forms
3. Greatest chemical and microbial stability compared to other oral dosage forms
4. Objectionable odor and taste can be masked by coating technologies
5. Flexible concept
6. Offer greatest precision and the least content uniformity
7. Easy to swallow with least hang up problems
8. Fit for large scale production
9. Bi-layer tablet is suitable for preventing direct contact of two drugs and thus to maximize the efficacy of combination of two drugs.

Various techniques for bilayer tablet[19-21]

1. OROS® push pull technology
2. L-OROS® tm technology
3. DUROS® technology.

Bi-layered tablets: Quality and good manufacturing practice requirements[22]

To produce a quality bi-layered tablet, in a validated and GMP way, it is important to select a bi-layered tablet press is capable of:

- Preventing capping and separation of the two individual layers that constitute the bi- layer tablet
- Providing sufficient tablet hardness
- Preventing cross contamination between the two layers
- Producing a clear visual separation between the two layers
- High yield
- Precise and individual weight control of the two layers.

Types of bi-layer tablet presses

1. Single-sided tablet press[23]
2. Double sided tablet press or "compression force" controlled tablet presses.

Table 1: Classification of mucoadhesive polymers

Criteria	Categories	Examples
Source	Semi- natural/ natural	Agarose, Chitosan
	Synthetic	Hyaluronic acid, Guargum, Na-alginate, Sodium CMC, HEC, HPMC, Carbopol
Solubility	Water- soluble	CP, HEC, HPC, HPMC, Sodium CMC, etc.
	Water-insoluble	Chitosan (soluble in dilute aqueous acids)
Charge	Cationic	Aminodextran, Chitosan, Trimethylated
	Anionic	Chitosan- EDTA, CP
	Non- ionic	Hydroxyethyl starch, HPC, PVA, PVP
Forces	Covalent	Cyanoacrylate
	Hydrogen bond	Acrylates, CP, PVA
	Electrostatic interaction	Chitosan

Classification[24,25]

In general, adhesive polymers can be classified by various ways as synthetic versus natural, water-soluble versus water insoluble and charged versus uncharged polymers. However, examples of the recent polymers classified in these categories are listed in below Table 1:

MATERIALS AND METHODS

Materials

Drug	Manufacturer
Losartan potassium	Dr. Reddy Labs (Gift Sample)
Polymer	
Carbopol 971	Noveon Chemicals, Bangalore
Hydroxypropyl methyl cellulose	Noveon Chemicals, Bangalore
Chemicals	
Dibasic calcium phosphate	Enar Chemicals Ltd., Ahmedabad
Sodium starch glycolate	Sujata Chemicals, Ahmedabad
Polyvinyl pyrollidone	Loba Chemie Pvt. Ltd. Mumbai
Talc	Loba Chemie Pvt. Ltd. Mumbai
Magnesium stearate	Finar Reagents, Mumbai
Hydrochloric acid	S.D. Fines Chemicals, Mumbai
Sodium hydroxide	S.D. Fines Chemicals, Mumbai
Potassium dihydrogen orthophosphate	S.D. Fines Chemicals, Mumbai
Instruments	
Compression machine (10 stations)	Electrolab, Mumbai
Digital weighing balance	Electrolab, Mumbai
Dissolution test system	Electrolab, Mumbai
Friabilator, EF- 2 (USP)	Electrolab, Mumbai
Hardness tester	Sartorius, Switzerland
pH –meter	Lab India, Baroda
Stability chamber	Thermolab, Mumbai
Tap density tester (USP)	JEL , Ahmedabad
Vernier calipers	Mahr Instruments, Ahmedabad
UV Spectrophotometer	Shimadzu

Methods

Pre-formulation

Bulk density (Db)[26]

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder (passed through standard sieve # 20) into a measuring cylinder and initial weight was noted. This initial volume was called the bulk volume. From this, the bulk density was calculated according to the formula mentioned below. It is expressed in g/ml and is given by

$$Db = M/Vb$$

Where, M and Vb are mass of powder and bulk volume of the powder, respectively.

Tapped density (Dt)[27]

It is the ratio of total mass of the powder to the tapped volume of the powder. Volume was measured by tapping the powder for 750 times and the tapped volume was noted if the difference between these two volumes is <2%. If it is more than 2%, tapping is continued for 1250 times and tapped volume was noted. Tapping was continued until the difference between successive volumes is <2 % (in a bulk density apparatus). It is expressed in g/ml and is given by

$$Dt = M/Vt$$

Where, M and Vt are mass of powder and tapped volume of the powder, respectively.

Hausner's ratio

Hausner's Ratio[28,29] is an ease of index of powder flow. It is calculated using the following formula:

Hausner's Ratio = Tapped density/Bulk density

Compressibility index

The compressibility index of the power was determined by Carr's compressibility index:

Carr's index (%) = {(D t – D b) × 100}/Dt

Carrs index	Type of flow
5–15	Excellent
15–18	Good
18–23	Fair to passable
23–35	Poor
35–38	Very poor

Angle of repose

Funnel method was used to measure the angle of repose of powder. The accurately weighed powders were taken in a funnel. The height of the funnel was adjusted in such

a way that the tip of the funnel just touched the apex of the heap of the powder (2.0 cm above hard surface). The powders were allowed to flow through the funnel freely onto the surface.

Angle of repose	Type of flow
<25	Excellent
25–30	Good
30–40	Passable
>40	Very poor

The diameter of the powder cone was measured and angle of repose was calculated using the following equation:

Angle of Repose θ = tan-1 H/R
Where
H = Height of the powder cone R = Radius of the powder cone

Preparation of bi-layer tablet[30-34]

The bilayer tablets of losartan potassium were prepared by the direct compression method. The drug, polymers and other excipients used for both immediate (IR) and SR layers were passed through sieve # 80 before their use in the formulation.[35-38]

Dose calculation[39]

For sustained drug release up to 30 h, the immediate dose of drug was calculated from total dose of losartan potassium ER tablet, which is 50 mg. According pharmacokinetic data.[40,41]

Dt = Dose (1 + 0.693 × t/t 1/2)

Where, Dt = Total dose, Dose = IR dose, t = Total time period for which SR is required, t1/2 = Half-life of drug. Half-life of losartan potassium ranges from 1.5 to 2.5 h.

For example,

1. Losartan potassium: 50 = Dose (1+ [0.693 ×30]/1. 5), Dose = 3.36 mg Losartan potassium
2. Losartan potassium: 50 = Dose (1+ [0.693 ×30]/2.5), Dose = 5.37 mg Losartan potassium.

Table 2: Determination of standard calibration curve of losartan potassium in acidic pH 1.2

Concentration (mcg/ml)	Absorbance (nm)
0.1	0.0318
0.2	0.0554
1	0.1221
2	0.2051
5	0.4511
10	0.9218

According to dose calculation, IR dose of drug can be taken in between range of 3.36 mg and 5.37 mg for the preparation of bi-layer tablets; thus 5 mg of Losartan potassium was taken in IR layer, and 45 mg of Losartan potassium was taken in SR layers.

RESULTS AND DISCUSSION

Determination of λ_{max} of losartan potassium [Figures 1-9]

Figures 10 and 11 exhibits the UV Spectrum of losartan potassium scanned according to the procedure given in the chapter IV. The absorbance spectra are characterized by maxima at 206 nm in both acidic and phosphate buffer (pH 1.2 and pH 6.8 medium) [Figures 12-14].

Preparation of calibration curve for losartan potassium

Figures 15 and 16 show the calibration curves of losartan potassium, which was obtained when concentration in mcg/ml [Table 2] was plotted against absorbance. It gave straight line that passes through the origin in both pH 1.2 and pH 6.8 mediums. The correlation coefficient has been determined and found to be 0.994 and 0.997, respectively.

Preparation of losartan potassium bilayer tablets and evaluation of different physical parameters [Figures 17-20].

Bi-layer tablets contain losartan potassium as active ingredient, PVP-K30 as a binding agent, Sodium starch glycolate as superdisintigrant, HPMC K4M and Carbopol 940-P as sustaining material and to retain the structure of tablets, dicalcium phosphate as filler, Mg- stearate, and talc as lubricant and glidant. The composition of the different bilayer tablets. Different batches of tablets were prepared varying the different sustaining components that were considered to have significant effect on drug release. These bilayer tablets as well as the powder blends were subjected to various in-process quality control tests for evaluation of their different physical parameters. These in-process quality control tests are very much important not only

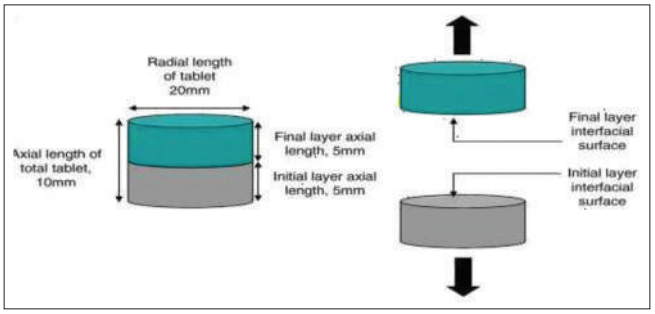

Figure 1: Diagram showing the definitions of the axial lengths, radial length, and interfacial fracture surfaces

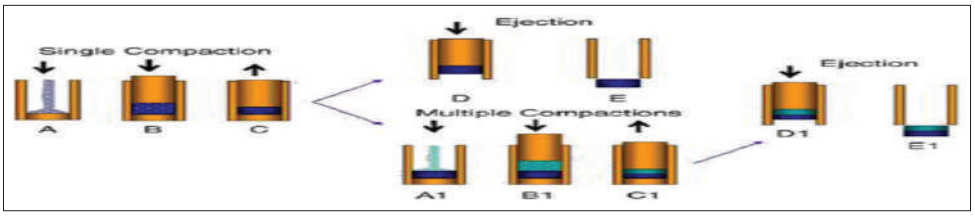

Figure 2: Filling of first layer, compression of first layer, ejection of upper punch. filling of second layer, compression of both layers

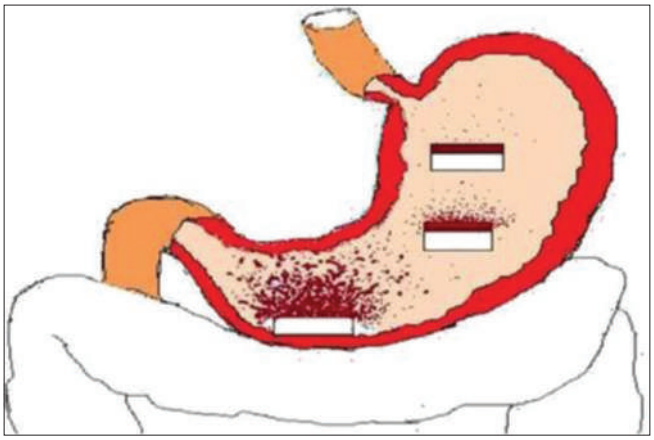

Figure 3: Figure showing immediate drug release from immediate release layer in stomach

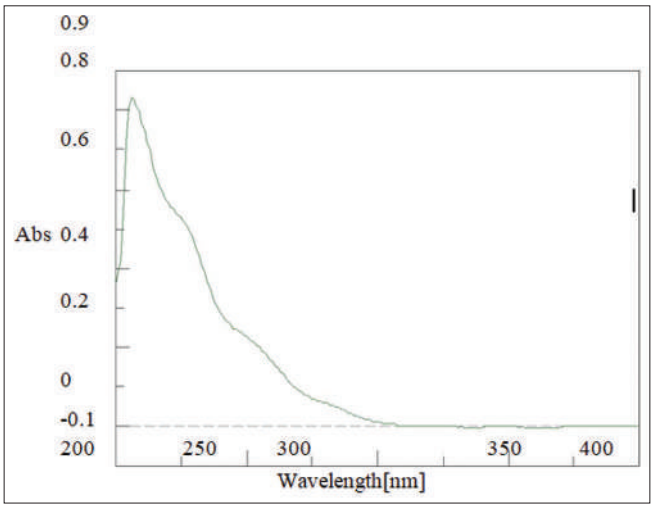

Figure 4: λ_{max} of losartan potassium in acidic pH 1.2

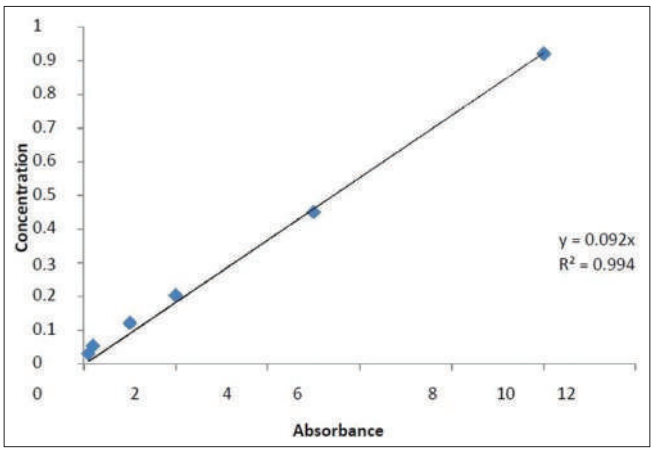

Figure 5: Standard calibration curve of losartan potassium in acidic Ph 1:2

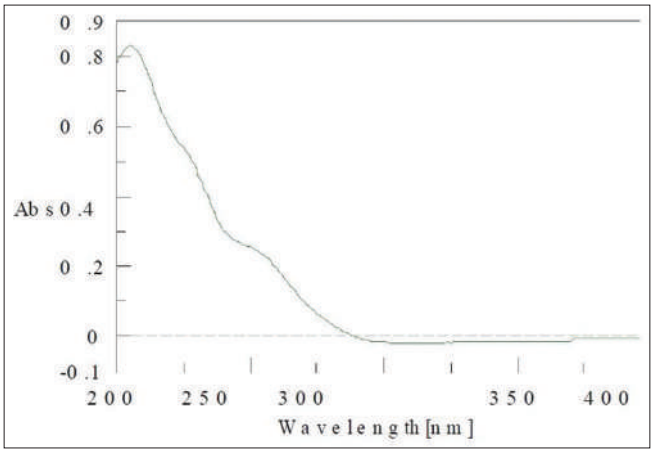

Figure 6: λ_{max} of losartan potassium in distilled water

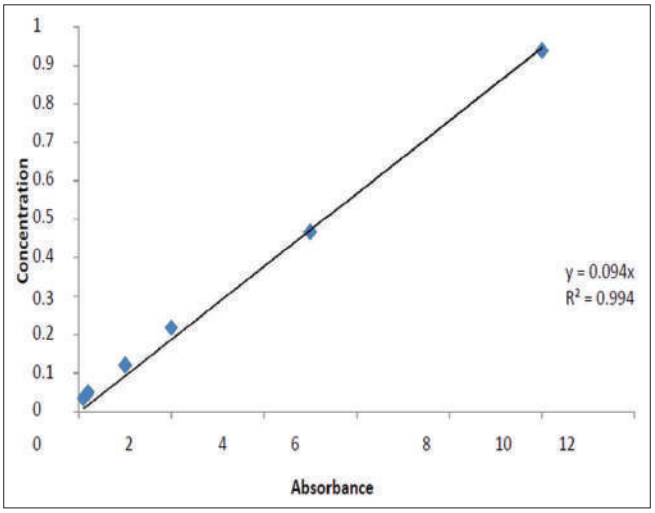

Figure 7: Standard calibration curve of losartan potassium in distilled water

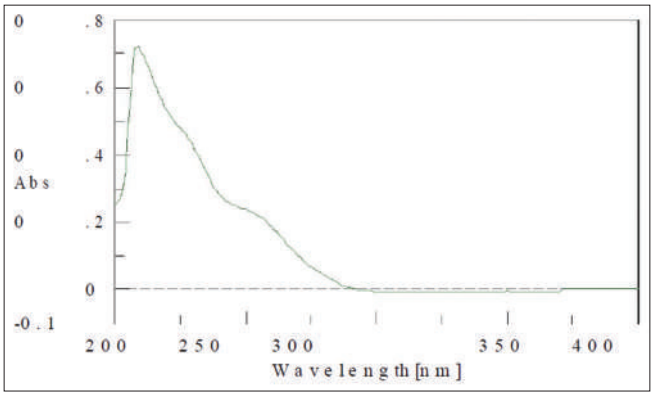

Figure 8: λ_{max} of losartan potassium in phosphate buffer pH 6.8

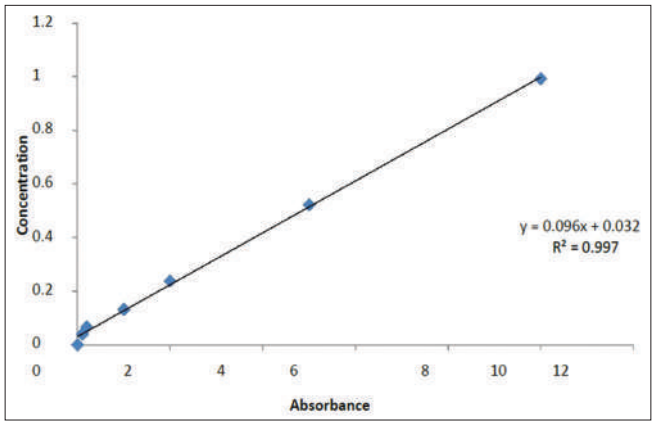

Figure 9: Standard calibration curve of losartan potassium in phosphate buffer pH 6.8

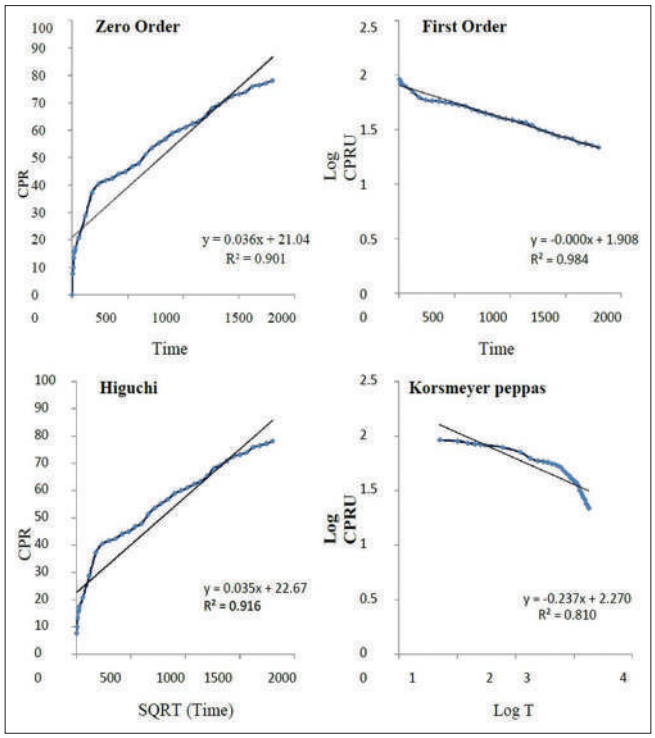

Figure 10: Different release kinetics of tables of formulation ME1

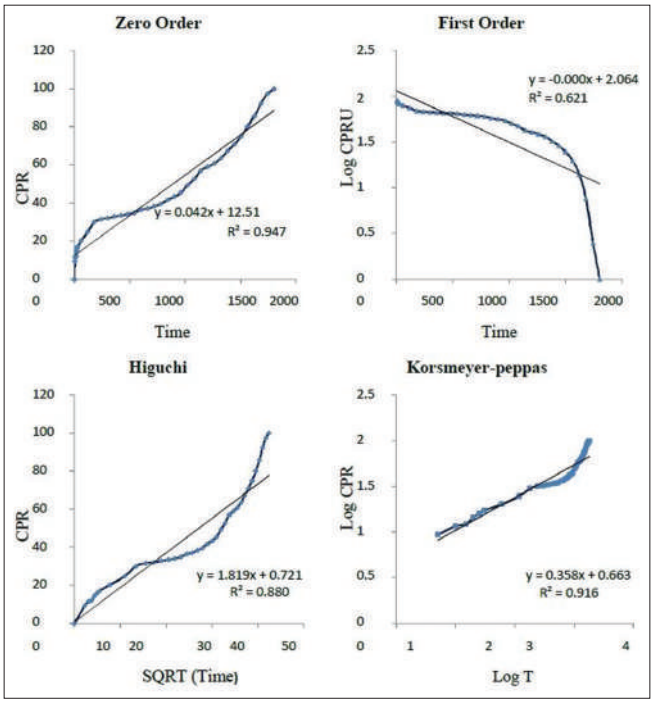

Figure 11: Different release kinetics of tables of formulation ME5

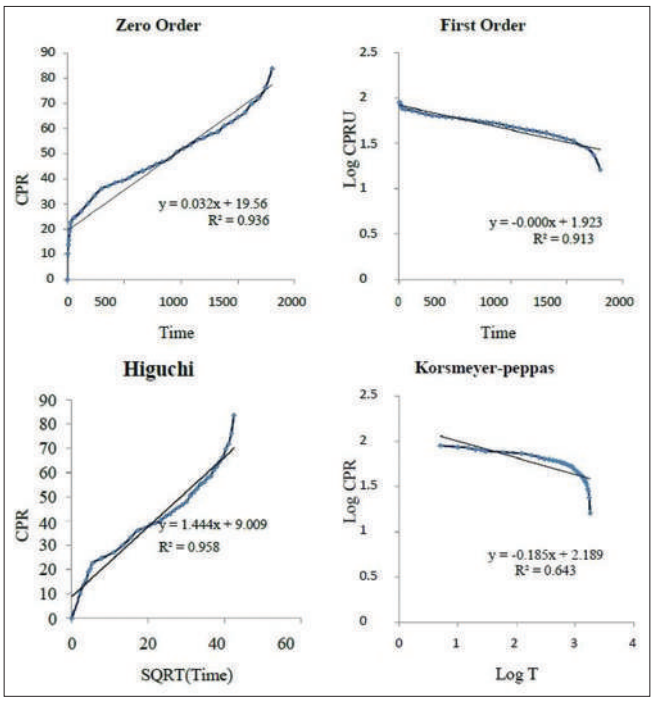

Figure 12: Different release kinetics of tables of formulation ME3

because these parameters determine the uniformity of flow properties of powders and uniformity of tablets in respect to weight, size, shape, and content but also they determine the suitability of tablets for further processing like *in vitro* release studies.

Bulk density and tapped density

Bulk density and tapped density of the losartan potassium of the optimized batches were determined as per the procedure described in Chapter IV. It was found from the results that bulk densities of all batches examined varied in the range from 0.68 to 0.73 g/ml and the tapped densities ranged between 0.81 and 0.93 g/ml.

Angle of repose

The method angle of repose described previously in Chapter IV is called a dynamic angle and is generally the preferred

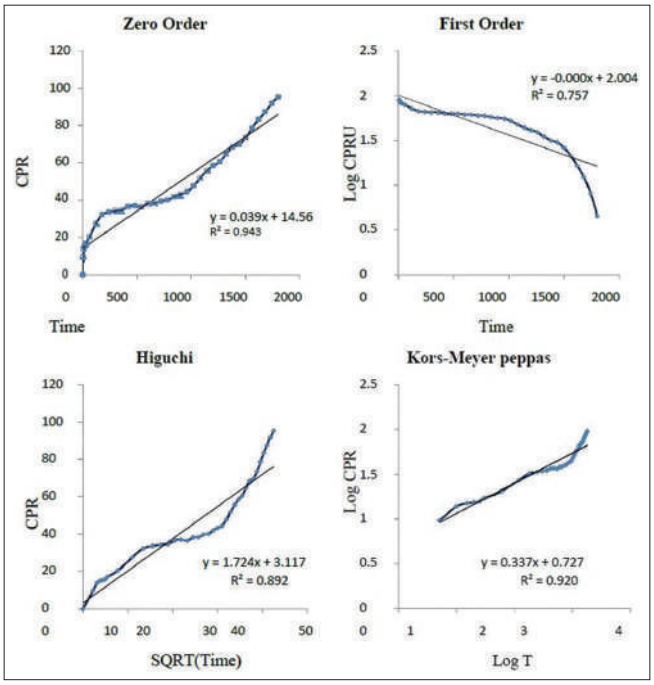

Figure 13: Different release kinetics of tables of formulation ME4

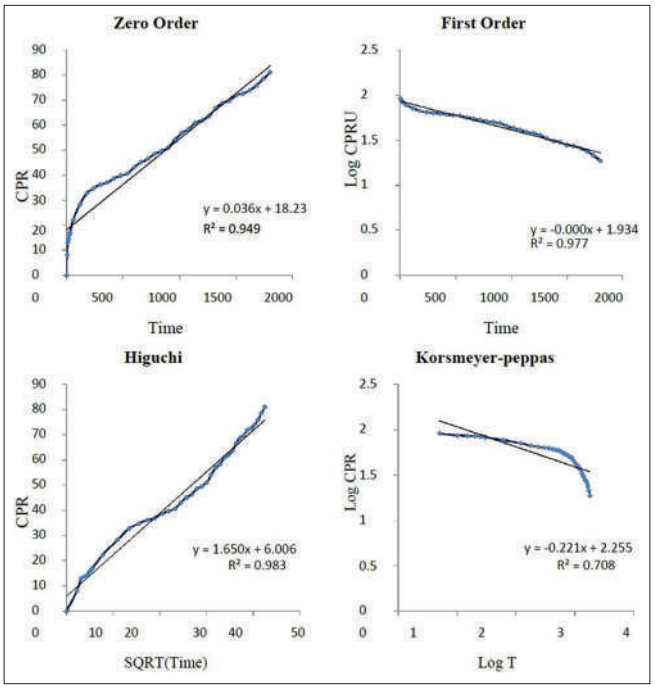

Figure 15: Different release kinetics of tables of formulation ME2

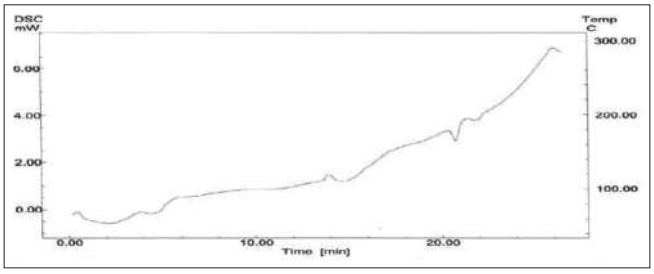

Figure 14: Differential scanning colorimetry result of losartan potassium + HPMC K4M

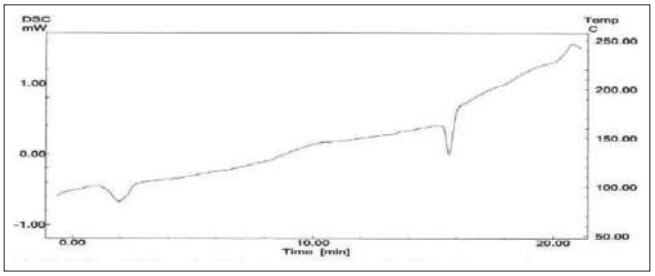

Figure 16: Differential scanning colorimetry result of losartan potassium

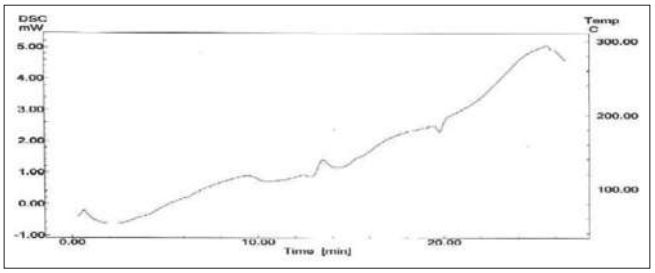

Figure 17: Differential scanning colorimetry result of losartan potassium + Carbopol 940P

means of measurement because it more closely mimics the manufacturing situation, in which the powder is in motion. Value of θ between 25 and 30 indicates good flow property. The θ values of the optimized batches. The values range in between 24.88 and 28.24, indicating that the powders have good flowing properties.

Compressibility index (I) and Hausner's ratio (R)

The flow ability of the powders was also indicated by compressibility index and Hausner's Ratio. Values of I below 15% usually give rise to good flow characteristics, the reading above 25% indicate poor flow ability (109). The I values of the optimized batches were found the range in between 16.04% and 22.25%.

Hauser Ratio (R) which is obtained as a ratio between tapped density and bulk density was found to fall in the range 1.19–1.29, indicating that the powders have free flowing properties.

Weight variation test

The maximum percentage weight variation that can be allowed for tablets according to USP is specified in table. Accordingly, if the tablet weight is between 130 and 324 mg, then the maximum % deviation allowed is ±7.5 %. The weight variation of the optimized batches. The % weight variation ranged between 1.36 and 1.48% and no tablets were found to be outside this range. Hence, the tablets

were statistically significant with respect to weight. Weight variation test is a satisfactory method of determining the drug content uniformity if the tablets were all or essentially all (90–95%) active ingredients, or if the uniformity of the drug distribution in the granulation or powder from which the tablets were made were perfect. Although the first criterion is not met in this study, every effort has been taken to uniformly mix the drug with other excipients. Hence, it is anticipated that the tablets which are uniform in respect to weight will also be uniform in respect to drug content.

Content uniformity

This is an important test to ascertain the uniformity of tablets with respect to drug content. The % variation of drug content should be within ±15%. In all the prepared batches on which the content uniformity tests were carried out, the content variation was very less, that is, within the compendia limits. Hence, as it was anticipated, the tablets are very much uniform in respect to drug content.

Thickness

Crown thickness uniformity is necessary not only for consumer requirement but also for packaging. Usually ±5% variation is permissible. The thickness of all bilayer tablets was tested by the method described in Chapter IV. It was observed that thickness of all tablets ranged between 3.43 and 3.47.

Hardness

The hardness of all losartan potassium tablets was tested by the method described in Chapter IV. It was found that hardness of prepared losartan potassium bilayer tablets varied between 6 and 8 kg/cm^2 for all the batches.

Friability test

During the compression of the powders, sufficient force was applied to get the final hardness of the tablet of around 6–8 kg/cm^2 hardness as measured in a Monsanto Tablet Hardness Tester. However, tablet hardness is not an absolute indicator of tablet strength. Friability test is done to ascertain whether the tablets are resistant to chipping and cracking during handling and/or subsequent processing. Weight loss should be <1% for good tablets. This test was performed on all the optimized batches of tablets as per the procedure given in Chapter 2. The loss % for all the batches was found to fall within the range of 0.14–0.33%.

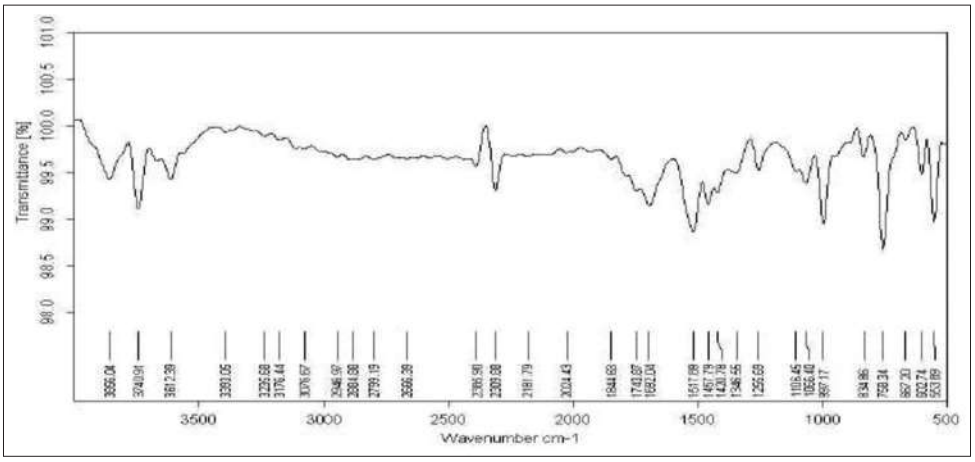

Figure 18: ATR + Fourier transform infrared curve of Losartan potassium

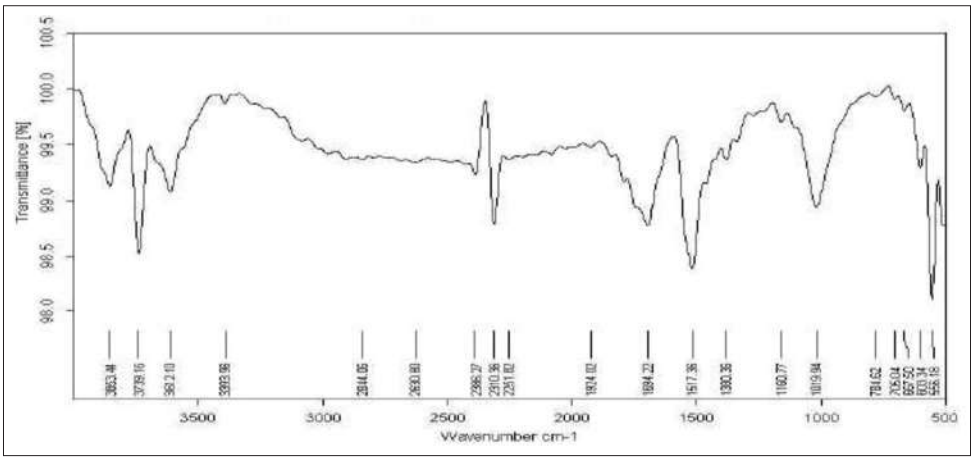

Figure 19: ATR + Fourier transform infrared curve of excipient (HPMC+Carbopol + PVP+Mg.stearate + Talc)

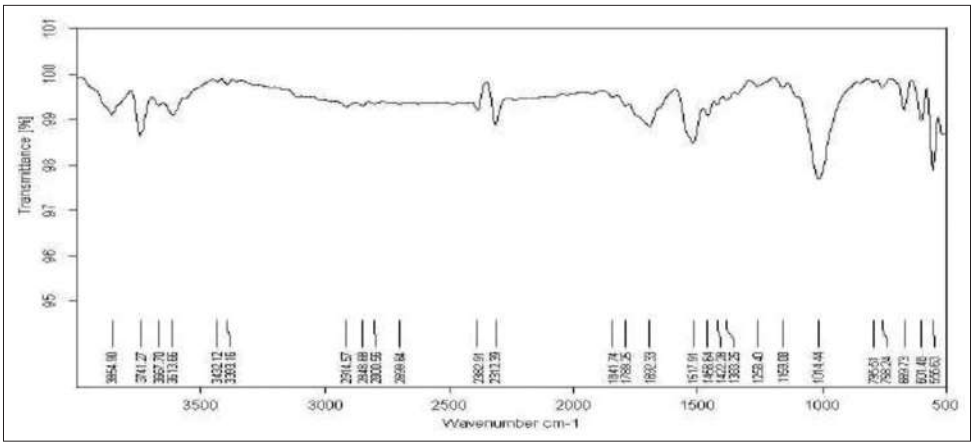

Figure 20: ATR + Fourier transform infrared curve of formulation ME5 (Drug + excipients)

Disintegration time of IR layer

The disintegration time of IR layer of all bilayer tablets was tested by the method described in Chapter IV. It was observed that disintegration time of all tablets ranged between 1 and 2 min.

CONCLUSION

The success of any research work depends on the results obtained there from and conclusion drawn therein, which could bring out the revealed or unrevealed or unexplored scientific explanations. The findings from any research work may further lead to better understanding, explanation, and profound knowledge in any specific area.

The present research was carried out to develop a bilayer tablet of losartan potassium using superdisintegrant sodium starch glycolate for fast release layer and combination of HPMC K4M and Carbopol 940-P for sustaining release layer. The tablets showed an initial burst release to provide the loading dose of drug followed by SR up to 30 h. This modified release bilayer tablets also reduced dosing frequency, increase the bioavailability and provide better patient compliance.

Finally, bi-layer tablet is improved beneficial technology to overcome the limitation of the single layered tablet. It is suitable for sequential release of two drugs in combination, separate two incompatible substances and also for SR tablet in which one layer is IR as initial dose and second layer is maintenance dose. The preparation of tablets in the form of multi layers is used to provide systems for the administration of drugs, which are incompatible and to provide controlled release tablet preparations by providing surrounding or multiple swelling layers.

REFERENCES

1. Dandare MS, Sarage RD, Bhaskaran S. Bilayer tablet: A novel approach for immediate release of Telmisartan and hydrochlorthaizide combination. Int J Pharm Tech 2012;4:3970-83.
2. Mukhopadhyay S, Goswami L, Satheesh Madhav NV, Upadhyaya K. Formulation and evaluation of floating bioadhesive tablets of ciprofloxacin hydrochloride by direct compression technique. Int J Pharm Pharm Sci 2010;2:113-5.
3. Kumar KK, Mahesh M, Sasikanth K. Design, Development and characterization of sustained release of metformin and gliclazide bi-layered tablets. Int J Biopharm 2010;1:67-71.
4. Medicine. Available from: http://www.Net.in. [Last accessed on 2013 Feb 10].
5. Derle D, Joshi O, Pawar A, Patel J, Jagadale A. Formulation and evaluation of buccoadhesive bi-layer tablet of propranolol hydrochloride. Int J Pharm and Pharm Sci 2009;1:206-12.
6. Walle T, Conradi EC, Walle UK, Fagan TC, Gaffney TE. The predictable relationship between plasma levels and dose during chronic propranolol therapy. Clin Pharmacol Ther 1978;24:668-77.
7. Cid E, Mella F, Lucchini L, Carcamo M, Monasterio J. Plasma concentrations and bioavailability of propranolol by oral, rectal and intravenous administration in man. Biopharm Drug Dispos 1986;7:559-66.
8. Kemken J, Ziegler A, Muller BW. Pharmacodynamic effects of transdermal bupranolol and timolol *in vivo*: Comparison of micro emulsions and matrix patches as vehicle. Methods. Find Exp Clin Pharmacol 1991;13:361-5.
9. Goodman M. The Pharmacology Basis of Therapeutics. London: McGraw-Hill Medical Publishing Division; 1884.
10. Kulkarni A, Bhatia M. Development and evaluation of regioselective bilayer floating tablets of atenolol and lovastatin for biphasic release profile. Iran J Pharm Res 2009;8:15-25.
11. Barhate SD, Rupnar Y, Rahane R, Patel MM. Formulation optimization of bilayer floating tablet of famotidine. Int J Pharm Bio Sci 2010;1:613-21.

12. Banu H, Sahariar MR, Sayeed MS, Dewan I, Islam A. Formulation development of bi-layer acetaminophen tablets for extended drug release. J Chem Pharm Res 2011;3:348-60.
13. Carla ML, José M, Sousa L, João FP, Paulo CC. Compressed matrix core tablet as a quick/slow dual-component delivery system containing ibuprofen. AAPS PharmSciTech 2007;8:76.
14. Kulakarni A, Bhatia M. Development and evaluation of bi-layer floating tablets of atenolol and lovastatin for biphasic release profile, Iran. J Pharm Res 2009;8:15-25.
15. Singh PK, Kumar S. Bilayer and floating bioadhesive tablets: Innovative approach to gastroretension. J Drug Deliv Ther 2011;1:32-5.
16. Nirmal J, Saisivam S, Peddamma C, Muralidharan S, Nagarajan M. Bilayer tablets of atorvastatin calcium and nicotinic acid: Formulation and evaluation. Chem Pharm Bull 2008;56:1455-8.
17. Ashok PH, Kumar TA. A novel approach of bi-layer tablet technology-a review. IRJP 2012;3:44-9.
18. Deshpande RD, Gowda DV, Mahammed N, Maramwar DK. Bi-layer tablets-an emerging Trend: A review. IJPSR 2011;2:2534-44.
19. Mehul P, Sockan GN, Mani T. Challenges in the formulation of bi-layered tablets: A review. IJPRD 2010;2:30-42.
20. Divya A, Kavitha K, Rupesh Kumar M. Complexity of pharmaceutical Science and Evaluation of Dosage. J Appl Pharm Sci 2011;1:43-7.
21. Shaikh TK, Gadhave MV, Jadhav SL, Gaikwad DD. Different techniques of bi-layer tablet: A review. Int J Univ Pharm Life Sci 2012;2:450-60.
22. Mehul P, Sockan GN, Kavitha K, Mani T. Challenges in the formulation of bi-layered tablets: A review. IJPRD 2010;2:30-42.
23. Miller SN, Hang MC, Johnston TP. The use of muc oadhesive polymers in buccal drug de livery. Adv Drug Del Rev 1996;57:1666-91.
24. Gu JM, Robinson JR, Leung SH. Binding of acrylic polymers to mucin/epithelial surfaces: Structure-property relations hips. Crit Rev Ther Drug Carr Syst 1998;5:21-67.
25. Lee JW, Park JH, Robinson JR. Bioadhesive-based dosage forms: The next generation. J Pharm Sci 2000;89:850-66.
26. Mohideen S, Jyothi B, Pavani S, Satyanarayana T, Suresh Kumar P, Navaneetha Krishn S. Formulation and evaluation of bilayered tablets of metformin hydrochloride and atorvastatin calcium. Int J Pharm Sci Rev Res 2011;10:130-4.
27. Panchal HA, Tiwari AK. Formulation, development and *In-vitro* evaluation of bilayer tablets of glibenclamide as immediate release and sustained release. Int J Pharm Sci Health Care 2012;2:1-18.
28. Wagh MP, Yewale CP, Zate SU, Kothawade PI, Mahale G. Formulation and evaluation of fast dispersible tablets of aceclofenac using different superdisintegrant. Int J Pharm Pharm Sci 2010;2:154-7.
29. Manikandan M, Kannan K. Design and evaluation of amlodipine besilate and atorvastatin calcium tablets. Res J Pharm Biol Chem Sci 2012;3:425-34.
30. Park K. A new approach to study mucoadhesion: Colloidal gold staining Int J Pharm 1989;53:209-17.
31. Smart JD. The basics and underlying mechanisms of mucoadhesion. Adv Drug Del Rev 2005;57:1556-68.
32. Park H, Amiji M, Park K. Mucoadhesive hydrogels effective at neutral pH. Proc Int Symp Cont Rel Bioact Mater 1989;16:217-8.
33. Nagai T, Konishi R. Buccal/gingival drug delivery systems. J Cont Rel 1987;6:353-60.
34. Sudhakar Y, Kuotsu K, Bandyopadhyay AK. Buccal bioadhes ive drug delivery-a promising option for orally less efficient drugs. J Cont Rel 2006;114:15-40.
35. USP. Drug information for Losartan potassium from United States Pharmacopoeia. USP29-NF 24:1280. United States: USP; 2007.
36. Shruti C, Gayathri VP, Sanjay KM. Release modulating hydrophilic matrix systems of losartan potassium: Optimization of formulation using statistical experimental design, Science direct. Eur J Pharm Biopharm 2006;66:73-82.
37. Chopra S, Patil GV, Motwani SK. Response surface methodology for optimization of Losartan potassium controlled release tablets. Sci Direct 2006;1:15-9.
38. Raju DB, Suresh John K, Varma MM. Formulation and evaluation of losartan potassium matrix tablets for oral controlled release. JOCPR 2010;2:130-5.
39. Shanmugam S, Chakrahari R, Sundaramoorthy K. Formulation and evaluation of sustained release matrix tablets of losartan potassium. Int J Pharm Tech Res 2011;3:526-34.
40. Vishnu MP, Bhupendra GP, Harsha VP, Karshanbhi MP. Mucoadhesive bilayer tablets of propranolol hydrochloride. AAPS PharmSciTech 2007;8:E77.
41. Pattanayak DP, Subash CD. Bilayer tablet formulation of metformin hydrochloride and glimepiride: A novel approach to improve therapeutic efficacy. Int J Drug Dis Herbal Res 2011;1:1-14.

Source of Support: Nil. Conflicts of Interest: None declared.