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A FORMULA FOR PREVENTING CARDIOVASCULAR DISEASE IN HEALTHY INDIVIDUALS AT RISK

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ABSTRACT

Patients suffering from cardiovascular disease are usually treated with concomitant administration of cholesterol lowering drugs such as atorvastatin, aspirin and beta blockers such as propranolol HCl. Therefore, the objective of this project is to formulate and evaluate a single oral tablet containing three drugs (atorvastatin, aspirin and propranolol HCl) as an alternative of giving the three drugs in three separate tablets. The interaction of aspirin with both chosen drugs was studied by using Fourier Transformer Infrared (FT -IR) spectroscopy and differential scanning calorimetry (DSC). The DSC traces depicted lowering of melting points of aspirin and atorvastatin by the action of each one on the other during heating. However, FT -IR results revealed that there is no molecular interaction between aspirin and either atorvastatin or propranolol HCl in the solid state. Quantitative detection of the three individual drugs in presence of each other in the prepared tablet was determined by using HPLC method. It was found that the HPLC method is sensitive, reproducible and valid for determination of atorvastatin, aspirin and propranolol HCl in the triple tablet form. Comparative dissolution studies were conducted to compare dissolution of the three drugs in the triple tablet to the individual commercial tablets. Successful comparative dissolution studies assured promising triple drug combination tablet for prevention of cardiovascular diseases and for improving patient compliance during treatment of cardiovascular diseases.

KEYWORDS: Atorvastatin, Aspirin, Propranolol HCl, Cardiovascular diseases and Preventive medicine.

INTRODUCTION

Preventive medicine is an interdisciplinary branch of medicine that focuses on the health of individuals, communities and the many factors influencing their health. Its goal is to protect, promote, and maintain health and well-being and to prevent disease, disability, and death. Chronic diseases, such as cancers, diabetes and heart disease are the major leading causes of death. This is why healthy habits, including eating well, exercising, and avoiding tobacco smoke are critical in helping individuals stay healthy, avoid disease, or minimize the effects of disease. This makes preventive medicine important in avoiding premature death. Preventive medicine can also lower annual costs spending on treatment of chronic diseases in the US.

Cardiovascular disease can imply a number of conditions such as blood vessel disease which is related to atherosclerosis. A heart attack occurs when the blood flow to a part of the heart is blocked by a blood clot. An ischemic stroke (the most common type of stroke) occurs when a blood vessel that feeds the brain gets blocked, usually from a blood clot. A hemorrhagic stroke occurs when a blood vessel within the brain bursts. This is most often caused by uncontrolled hypertension. Heart failure, sometimes called congestive heart failure, means the heart isn't pumping blood as well as it should Arrhythmia refers to an abnormal heart rhythm (Bradycardia or Tachycardia). There are various types of arrhythmias. The heart can beat too slow, too fast or irregularly. Heart valve problems, when heart valves don't open enough to allow the blood to flow through as it should, a condition called stenosis results. When the heart valves don't close properly and thus allow blood to leak through, it's called regurgitation. If the valve leaflets bulge or prolapse back into the upper chamber, it's a condition called prolapse.

The medications prescribed in the wake of a cardiac event can aid in recovery and work to prevent another stroke or heart attack. There are three categories of drugs that have been used for treatment of various cardiovascular disease which are anti-platelets aggregation drugs such as aspirin, cholesterol lowering agents such as statins and antihypertensive drugs such as beta blocker agents.

Aspirin was reported by large well-conducted studies to reduce the risk of heart attack in people without established cardiovascular disease [Baigent et al., 2009; Raju et al., 2011]. In addition, the American Heart Association (AHA) most recent recommendation (2016) clearly states that "People at high risk of heart attack should take a daily low-dose of aspirin (if told

to by their healthcare provider) and that heart attack survivors regularly take low-dose aspirin".

Atorvastatin, a member of the statin group has been shown by a major study published by Cochrane Library to provide primary prevention of a first event in healthy individuals at high risk of CVD [Fiona et al., 2013]. In addition, the AHA guideline recommends statin therapy for "people without cardiovascular disease who are 40 to 75 years old and have a 7.5 percent or higher risk for heart attack or stroke within 10 years" [Paul et al., 2013].

Propranolol is a member of a blood pressure lowering group called β blockers. The use of blood pressure lowering drugs was reported by a large meta-analysis study published in the british medical Journal to effectively prevent cardiovascular diseases in people with and without cardiovascular disease history [Law et al., 2009]. We believe introduction of this Beta blocker is very essential in the prepared tablets because Beta blocker is aimed at maintaining reasonable blood pressure in healthy individuals since elevated blood pressure is known to be a predisposing factor for stroke

It is clinically recommended to give patients who already suffered one incidence of myocardial infarction the three drugs (at low dose aspirin and therapeutic dose statin and therapeutic dose beta blocker) to prevent recurrence of myocardial infarction. Our composition on the other hand is proposed to be given (at low dose of the three drugs) in one tablet to healthy individuals to prevent myocardial infarction and other cardiovascular events such as stroke from happening for the first time. The use of these three drugs is supported by published clinical studies for use in prevention and treatment of cardiovascular events [Baigent et al., 2009].

The main aim of this study was to design and evaluate a formula containing the three drugs in single tablet dosage form to prevent cardiovascular disease (CVD) for healthy adult individuals at high risk.

MATERIALS AND METHODS

Materials

Atrovastatin was a gifted from Aljazera Pharmaceutical company, Riyadh, Saudi Arabia. Propranolol hydrochloride was a gift from Riyadh Pharma company, Riyadh, Saudi Arabia. Aspirin was purchased from E. Merck, D-6100, Darmstadt, Germany. Phosphoric acid,

Potassium dihydrogen phosphate and Hydrochloric acid were purchased from Sigma chemical, St. Louis, MO., USA. Acetonitrile was purchased from BDH Chemicals Ltd., Poole, England. Avicel PH 102 was purchased from Winlab, UK. Sodium starch glycolate, and magnesium stearate were purchased from Riedel-De Huen AG, Seeleze, Hannover. All solvents used for chromatographic determinations were of HPLC grade. All other reagents and solvents were of analytical grade. The following commercial brands (innovators) were used for comparison (Aspocid® tablets containing aspirin 100 mg form CID Pharmaceuticals Egypt, Inderal® tablets containing 10 mg propranolol HCl from AstraZeneca and Lipitor tablets containing 10 mg atorvastatin from Pfizer).

Preparation of physical mixtures of aspirin, propranolol HCl and atorvastatin

Ternary physical mixtures of Aspirin with both Atrovastatin and Propranolol HCl were prepared by ordered mixing using mortar and pestle. Binary physical mixtures of aspirin with either atorvastatin or propranolol HCl were prepared in different weight ratios by the same above mentioned method. The samples were investigated by using FT -IR and DSC methods.

Compatibility assuring test using differential scanning calorimetry (DSC)

DSC measurement of each drug and their physical mixtures was carried out using Shimadzu DSC -60 with TA -60 WS (Japan) equipped with software computer program. Running was operated under nitrogen purge gas with the rate 40-50 ml/min, and heating rate of 10 ºC/min. The weights of the samples were in the range of 2-5 mg. The temperature range of DSC runs was from 25ºC to 220ºC. The DSC thermograms were recorded for samples sealed in aluminum pans and indium was used as standard for calibrating the instrument. The peak temperature of melting of each sample and the heat of fusion were determined from DSC traces by thermal analysis program.

Compatibility assuring test using Fourier Transformer Infrared (FT-IR) spectroscopy

FT-IR spectrophotometer (Nicolet 380 FT-IR, Thermo Scientific, USA) was used to obtain the spectra of aspirin, atorvastatin, propranolol HCl, and their physical mixtures by KBr disc method. Polystyrene disc was used as scanning reference before measurement of samples by FT-IR spectrophotometer in the range of wave number 4000 - 400 cm^{-1}. The Sample mixtures were prepared in a smooth agate mortar and compressed into a disc of 13-mm diameter using hydraulic press.

Formulation of the triple tablets

Triple tablets containing aspirin (100 mg), atorvastatin (10 mg) and propranolol HCL (10 mg) were prepared by the direct compression technique. Components of the formulae shown in Table 1 were mixed in turbula mixer (type S27, Erweka, Apparatebau, Germany) and then directly compressed into tablets using a single punch tablet machine (type EKO, Erweka, Apparatebau, Germany) using 8 mm concave punches.

Tablets' crushing strength was kept within the range of 6-8 kp and tablet weight to be around 400 mg. Avecil PH 102 is used as diluent, magnesium stearate as lubricant, dibasic sodium phosphate to enhance the dissolution of atorvastatin and cross povidone as disintegrant.

Evaluation of the Prepared Triple Tablets

The obtained tablets were evaluated with regard to uniformity of weight and content, disintegration time, and friability according to B.P. Friability of 10 tablets were measured using friability tester (type TA3R, Erweka Apparatebau, Germany). Hardness of tablets was measured using hardness tester (type TBH 28, Erweka, Apparatebau, Germany).

HPLC analysis method

The HPLC method consisted of a waters isocratic liquid chromatography system (Waters, Boston, Mass., USA) containing Waters 717 plus autosampler, Waters 1525 binary HPLC pump, Waters 2487 dual absorbance detector. All analyses were conducted at ambient temperature. Separations were performed on symmetry C18, 5 µm, 4.6 X 150 mm waters column. pH of the mobile phases was adjusted by phosphoric acid. The chromatographic condition for the assay of each drug is shown in Table 2. The mobile phases were membrane filtered (Millipore, 0.45 µm pore size) and degassed using Nexul ultrasonic, Kodo technical Co., South Korea. The eluent was monitored at 261nm for detecting atorvastatin, 230 nm for detecting aspirin and 235 nm for detecting propranolol HCl. Calibration curves, based on the average of peak height of various concentrations for each drug, were employed to evaluate the drug content or amount dissolved from the tablets. Standard solutions were assayed and calibration curves were constructed before analysis of each sample to ensure reproducibility of the HPLC method.

Dissolution studies

Dissolution study of the individual commercial tablets and the triple tablets containing aspirin, propranolol HCl and atorvastatin were performed using USP dissolution apparatus 1

(Caleva Ltd., Model 85T), at 100 rpm in dissolution medium of 750 ml of 0.1N HCl. The temperature was maintained at 37 ± 0.5ºC. At specified time intervals, 5 ml was withdrawn and substituted by freshly prepared dissolution medium maintained at the same temperature. The amount dissolved of each component in tablets was determined by HPLC method. Each release was run in triplicate.

RESULTS AND DISCUSSION

Figure1 depicts DSC curves of each drug alone and their physical mixture. DSC traces of the studied drugs gave endothermic peaks at 145.97, 159.1 and 166.74ºC, which are due to the melting of aspirin, atorvastatin and propranolol HCl, respectively. On the other hand, DSC curve of physical mixture showed broad endothermic peak at 120.12. The broad endothermic peak can be attributed to the fusion of propranolol HCl and atorvastatin with aspirin at high temperature. This may be due to the effect of each drug on the other at higher temperature.

To conform that there is no chemical interaction between the three drugs in the triple tablet, FT-IR spectral analysis was conducted.

FT-IR spectra of aspirin alone, propranolol HCl alone, atorvastatin alone and their physical mixture (1:1:1 weight ratio) are shown in figures 2A, 2B, 2C and 2D respectively.

Figure 2A shows FT-IR spectra of aspirin alone. FT-IR spectrum of aspirin alone dedicated its characteristic peaks, from which the stretching vibration of two carbonyl bands at 1754 and 1689.35 cm^{-1} of acetyl and carboxylic groups, respectively, and stretching vibration of -CH- of benzene ring at 1605.5 cm^{-1}. The above characteristic peaks of aspirin are not affected by presence of atorvastatin and propranolol HCl in its ternary mixture and they appeared at 1753.74, 1693.4 and 1605.6 cm^{-1} (Figure 2D). These results revealed that there is no molecular interaction between aspirin and either atorvastatin or propranolol HCl in the solid state.

Figure 2B shows the IR spectra of propranolol HCl alone. Propranolol HCl gives the peaks in IR spectrum nearby at 2965 cm^{-1} due to the presence of a secondary amine group, 3283 cm^{-1} due to the hydroxyl group (secondary), the aryl alkyl ether display a stretching band at 1267.27 cm^{-1}. Figure 2D revealed the presence of peaks at 2964.69 cm^{-1}, 3282.95 cm^{-1}, 1267.27 cm^{-1}. Frequencies of functional groups of pure drug remained intact in physical mixture containing different drugs.

The IR spectra of pure atorvastatin (Figure 2C) showed characteristic peaks at 2971.69 cm^{-1} (C-H– stretching), 1313.56 cm^{-1} (C-N –stretching), 1576.34 cm^{-1}(C=O – stretching amidic group), 3364 cm^{-1} (N-H - stretching), Figure 2D revealed the presence of these peaks in physical mixture containing different drugs at the same wave numbers. Conclusively, the chosen three drugs are compatible when mixed together in the solid state.

Tablet Evaluation

The tablets containing the three drugs was successfully prepared using direct compression method. The manufactured tablets were evaluated for their weight and content uniformity, hardness, as well as friability. The weight of the tablets in the prepared formulation was found to be in the range of 0.396 to 0.410 g and the content of each drug was in range of 90-110% of the labled amount. The average tablet hardness was found to be 5.2 - 6.2 kp. Moreover, the tablets exhibited acceptable friability that is less than 1%.

Dissolution studies

Figures 3A, 3B & 3C show the dissolution profiles of aspirin, propranolol HCl and atorvastatin from the prepared triple tablets and from commercial tablets in 0.1N HCl at 37ºC. To enhance the dissolution of atorvastatin, sodium phosphate dibasic was incorporated into the triple tablets to raise the micro environmental pH. It was evident that all forms of atorvastatin were dissolved better, if the tablet was capable of increasing the pH value to pH $\geq$ 6, in another word a pH value equal to or greater than pK_a of the drug. This was achieved by incorporation of dibasic sodium phosphate. The amount dissolved as % within two hours in 0.1N HCl for aspirin reached 98%, for propranolol HCl reached 96% and for atorvastatin was 51%. The comparative dissolution data was calculated as similarity factor (f2) between drug dissolution from the triple tablet in comparison to drug dissolution of from individual commercial tablets. The dissolution similarity factor (f2) was calculated as 79%, 60%, 50% for aspirin, propranolol HCl and atorvastatin, respectively.

Results of the comparative dissolution study assures successful formulation of the chosen three drugs in a single triple tablet with satisfactory dissolution rate of the three drugs in comparison to the individual commercial tablets.

Table 1: Composition of the triple therapy tablet.

Composition (mg)	
Aspirin	100
Propranolol HCl	10
Atrovastatin	10
Dibasic sodium phosphate	130
Cross povidone	20
Avicel PH 102	130
Magnesium stearate	4
Tablet weight (mg)	404

Table 2: Chromatographic condition for the assay methods for each drug in the triple tablets.

Parameters	Aspirin	Propranolol HCl	Atrovastatin
Mobile phase composition	water : acetonitrile	10 mM phosphate : acetonitrile	water : acetonitrile
Mobile phase ratio (v/v)	2:1	68:32	85:15
pH of the mobile phase	3	3.5	4.5
Flow rate (ml/min)	1	1	1.5
Retention time (min)	4.6	7.5	6.1
Wave length (λ_{max}) nm	230	235	261
Detection limit (µg/ml)	2.5	2.5	2

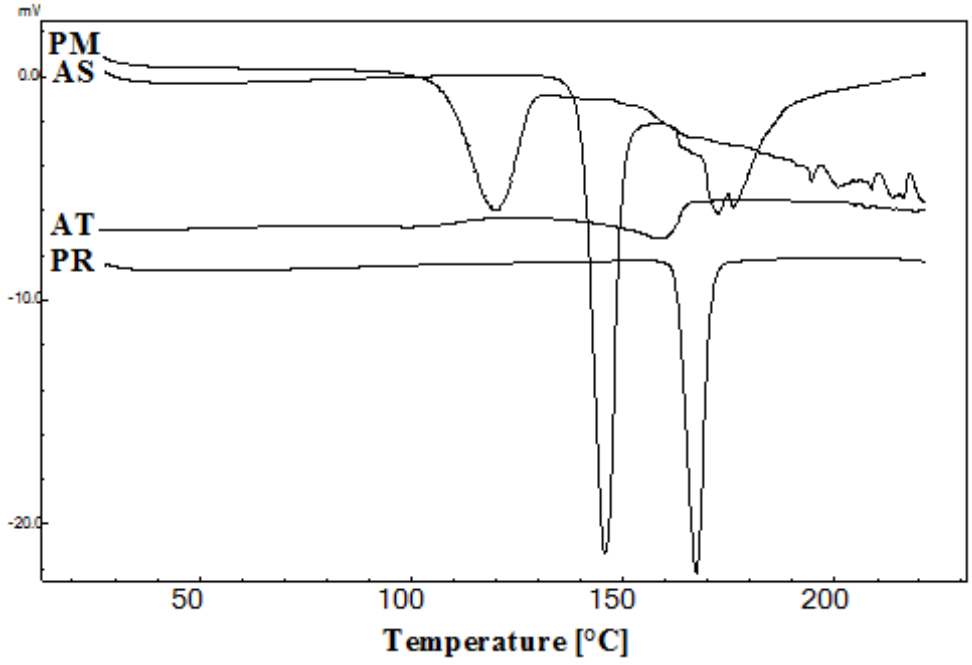

Figure 1: DSC Thermograms of Aspirin (AS), Propranolol HCl (PR), Atorvastatin (AT) and their physical mixture (PM).

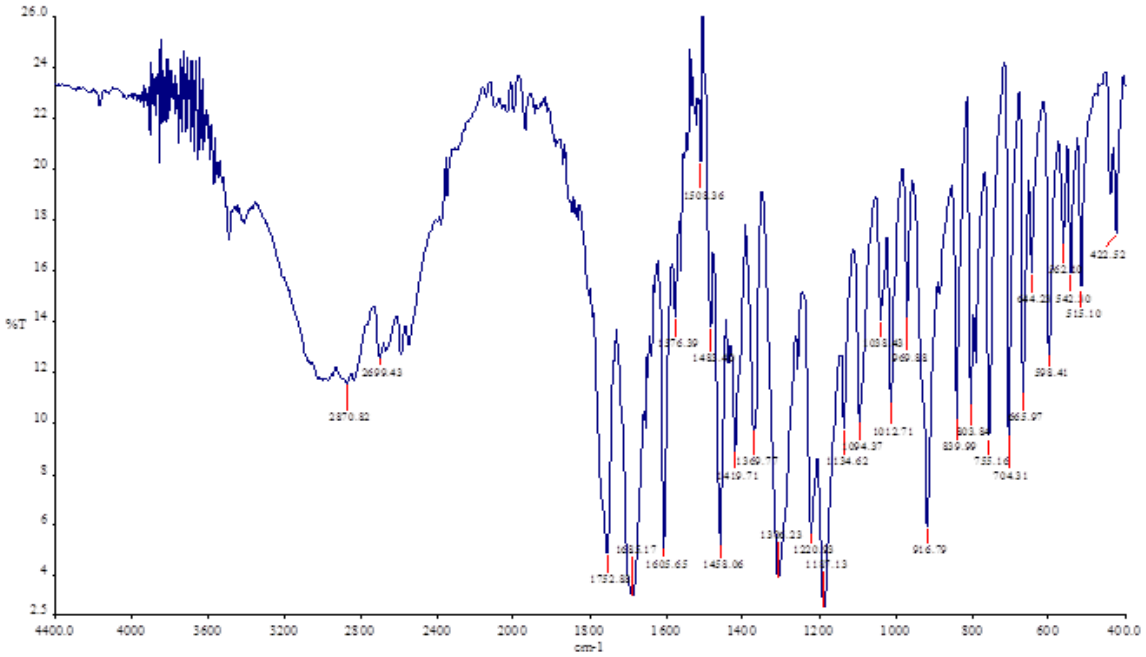

Figure 2A: FT-IR spectra for Aspirin.

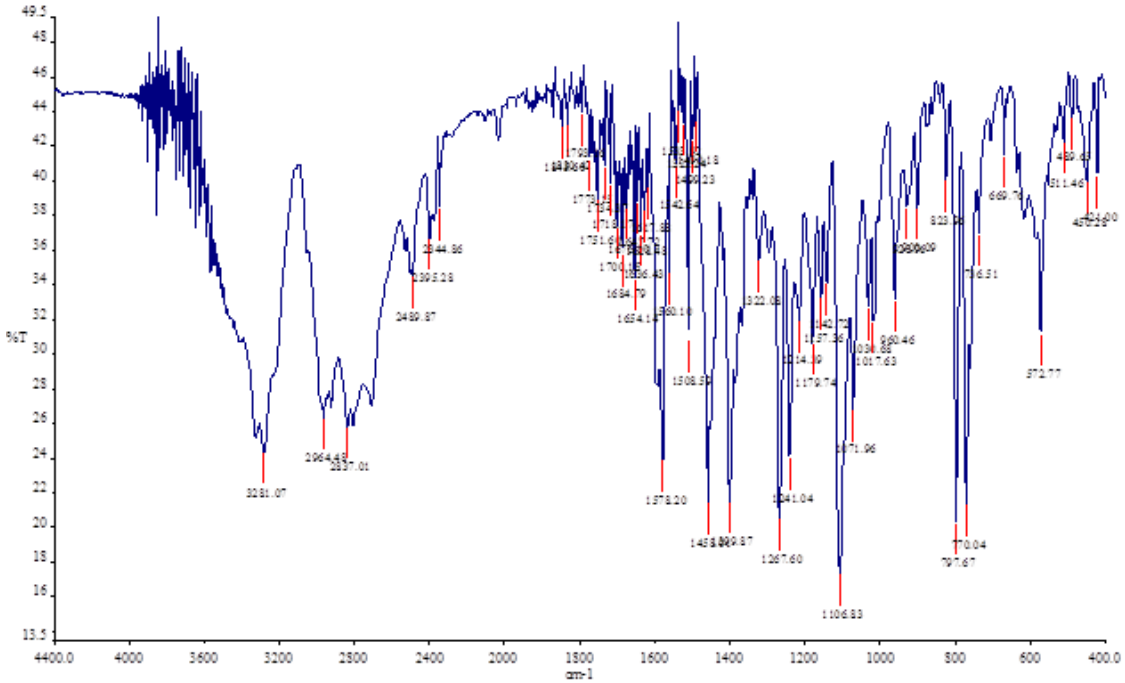

Figure 2B: FT-IR spectra Propranolol HCl.

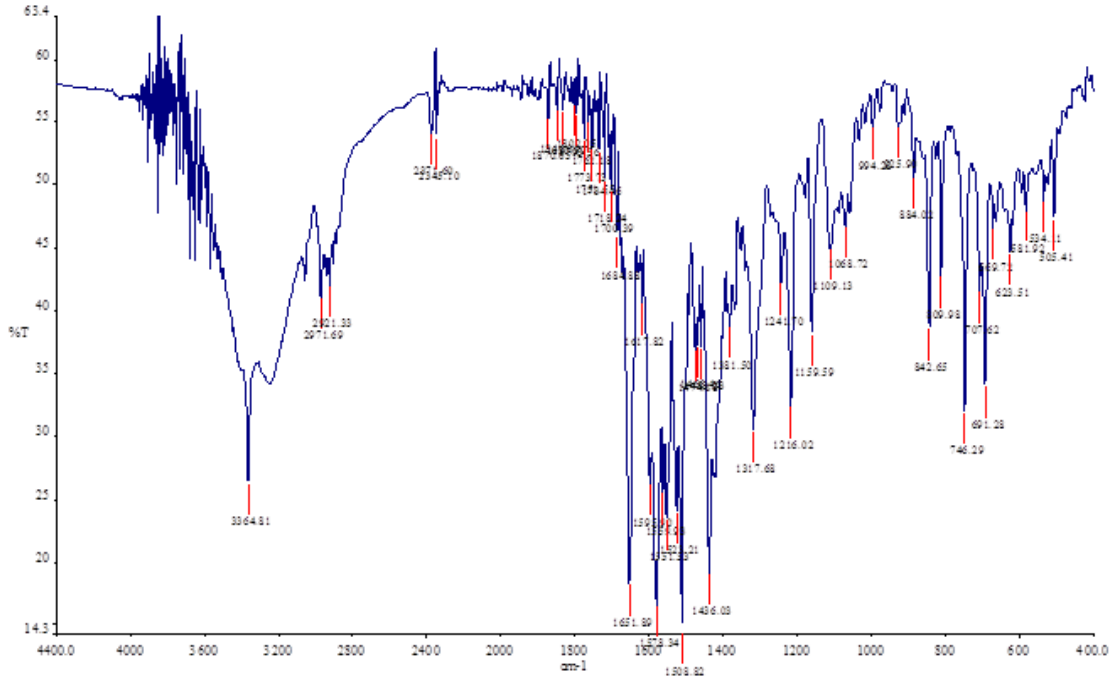

Figure 2C: FT-IR spectra Atorvastatin.

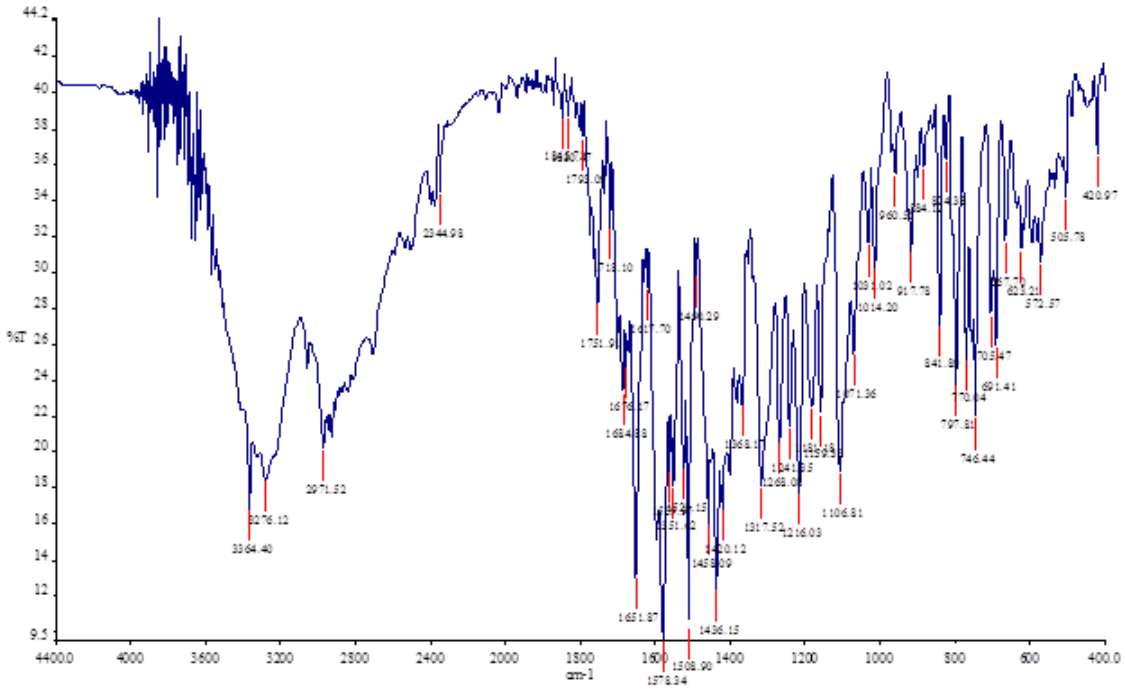

Figure 2D: FT-IR spectra for physical mixture.

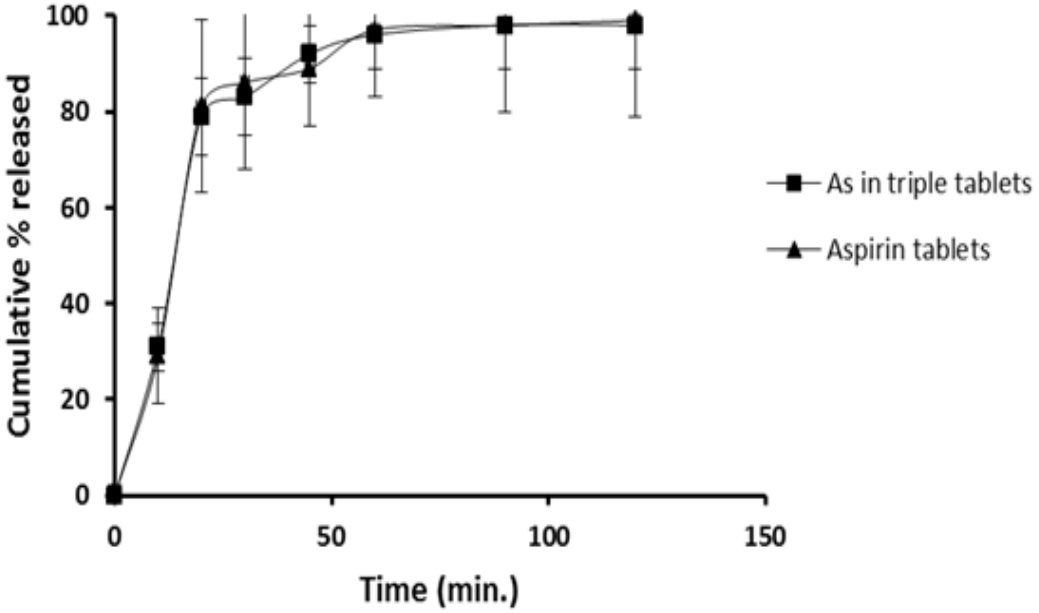

Figure 3A: Dissolution profile of Aspirin (AS) in 0.1 N HCl from triple tablets and Aspocid® tablets.

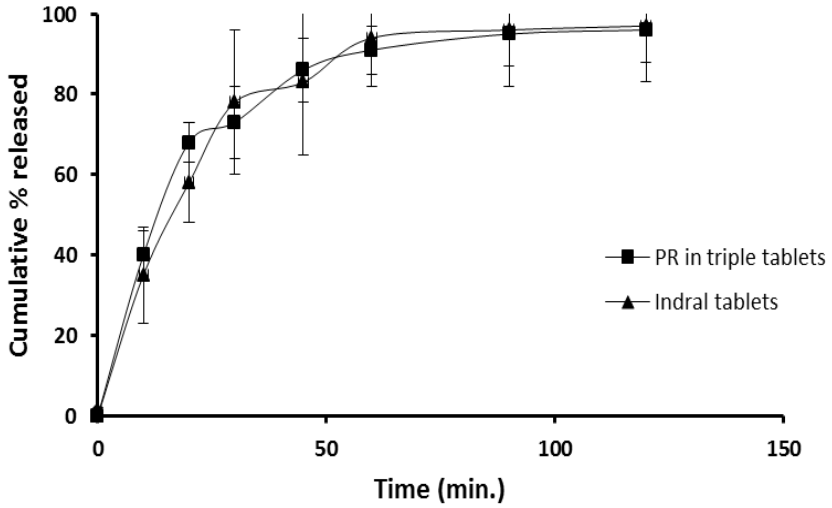

Figure 3B: Dissolution profile of Propranolol HCl (PR) in 0.1 N HCl from triple tablets and Indral® tablets.

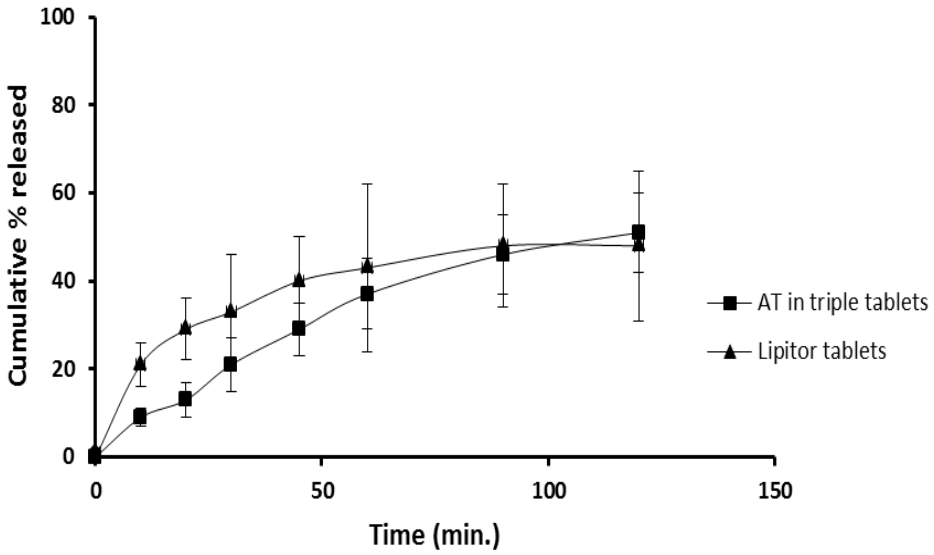

Figure 3C: Dissolution profile of Atorvastatin (AT) in 0.1 N HCl from triple tablets and Lipitor® tablets.

CONCLUSION

We believe the prepared formulation containing three drugs intended to be used for prevention of cardiovascular diseases in healthy adult individuals aged 50 years and older specially whom at risk.

Conflict of Interest

The authors declare that they have no conflict of interest.

REFERENCES

1. Ahmed, M.O., 2000. Interaction of ibuprofen with certain drugs, Paper presented at the 2 International nd conference of pharmaceutical sciences and technology, Alexandria, October 25-27.
2. Antman, E.M., D.T. Anbe, P.W. Armstrong, 2004. ACC/AHA Guidelines for the Management of Patients with ST-Elevation Myocardial Infarction- Executive Summary: A Report of the ACC/AHA Task Force on Practice Guidelines. Circulation, 110: 588-636.
3. Baigent C, Blackwell L, Collins R, Emberson J, Godwin J, Peto R, Buring J, Hennekens C, Kearney P, Meade T, Patrono C, Roncaglioni MC, Zanchetti A. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomized trial, The Lancet, 2009; 373: 1849-1860.

4. Braunwald, E., E.M. Antman, J.W. Beasley, 2002. ACC/AHA guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction: (Committee on the Management of Patients with unstable Angina). Circulation, 106: 1893-900.
5. Fiona Taylor, Mark D. Huffman, Ana Filipa Macedo, Theresa HM Moore, Margrat Burke, George Davey Smith, Kristen Ward, Shah Edbrahim. Statins for the primary prevention of cardiovascular disease. The Cochrane Library (2013).
6. Frishman, W.H., A. Cheng, 1999. Secondary prevention of myocardial infarction: role of beta-adrenergic blockers and angiotensin-converting enzyme inhibitors. Am Heart J., 137: S25-S34.
7. Fuster, V., M.L. Dyken, P.S. Vokonas, C. Hennekens, 1993. Aspirin as a therapeutic agent in cardiovascular disease. Special Writing Group. Circulation, 87: 659–675. Guidelines. Circulation, 110: 588-636.
8. Guillory, K., S.C. Hwang, J.L. Lach, 1969. Interaction between pharmaceutical compounds by thermal methods. J. Pharm. Sci., 58: 301-308.
9. Hennekens, C.H., J.E. Buring, P. Sandercock, R. Collins, R. Peto, 1989. Aspirin and other antiplatelet agents in the secondary and primary prevention of cardiovascular disease. Circulation, 80: 749-756.
10. Herlitz, J., M. Dellborg, B.W. Karlson, J. Lindqvist, T. Karlsson, W. Sanden, M. Sjolin, H. Wedel, 2001. Changes in the use of medications after acute myocardial infarction: possible impact on mortality after myocardial infarction and long-term outcome. Coronary Artery Disease, 12: 61-67.
11. Hippisley-Cox, J., C. Coupland, 2005. Effect of combinations of drugs on all cause mortality in patients with ischaemic heart disease: nested case-control analysis. B.M.J., 330: 1059-63.
12. Hognestad, A., K. Dickstein, E. Myhre, S. Snapinn, J. Kjekshus, 2004. Optimal Investigators: Effect of combined statin and beta-blocker treatment on one-year morbidity and mortality after acute myocardial infarction associated with heart failure. American Journal of Cardiology, 93: 603-606.
13. Iglesias, R., C. Taboada, C. Souto, R. Martinez-pacheco, J.L. Gomez-Amoza, A. Concheiro, 1998. Development of tablets for controlled joint release of nifedipine and atenolol. Drug Develop. Ind. Pharm., 24: 835-840.
14. Jun, S.W., M.S. Kim, J.S. Kim, H.J. Park, S. Lee, J.S. Woo, S.J. Hwang, 2007. Preparation and characterization of simvastatin/hydroxypropyl-b-cyclodextrin inclusion

complex using supercritical antisolvent (SAS) process. E. J. Pharm. Biopharm., 66: 413-421.

15. Krause, M.W., M. Massing, A. Kshirsagar, W. Rosamond, R.J. Simpson, 2004 Combination therapy improves survival after acute myocardial infarction in the elderly with chronic kidney disease. Renal Failure, 26: 715-725.
16. Law MR, Morris JK, Wald NJ. Use of pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomized trials in the context of expectations from prospective epidemiological studies, BMJ, Vol. 338 (2009).
17. Manson, J.E., M.J. Stampfer, G.A. Colditz, W.C. Willett, B. Rosner, F.E. Speinzer, C.H. Hennekens, 1991. A prospective study of aspirin use and primary prevention of cardiovascular disease in women. J.A.M.A., 266: 521-527.
18. Oberoi, L.M., K.S. Alexander, A.T. Riga, 2005. Study of interaction between ibuprofen and nicotinamide using DSC, spectroscopy, and microscopy; and formulation of a fast-acting and possibly better ibuprofen suspension for osteoarthritis patients. J. Pharm. Sci., 94: 93-101.
19. Paul M. Ridker, Nancy R Cook., Statins: New American guidelines for prevention of cardiovascular disease, The Lancet, 2013; 382: 1762-1765.
20. Peto, R., R. Gray, R. Collins, K. Wheatley, C. Hennekens, K. Jamirozik, C. Warlow, B. Hafner, E. Thompson, S. Norton, 1988. Randomized trial of prophylactic daily aspirin in British male doctors. Br. Med. J., 296: 313-316.
21. Raju N., Sobieraj-Teague M., Hirsh J., O'Donell M. Eikelboom J., Effect of aspirin in the primary prevention of cardiovascular disease. Am. J. Med., 2011; 124(7): 621-9.
22. Sakata, Y., E. Tanabe, T. Sumikawa, S. Shiraishi, Y. Tokudome, M. Otsuka, 2007. Effects of solid state reaction between paracetamol and cloperastine HCl on the pharmaceutical properties of their preparations, Int. J. Pharm., 335: 12-19.
23. Saleh, S.I., S.H. Khider, S.M. Ahmed, T.M. Jackanicz, H.A. Nash, 2003. Estradiol-progesterone interaction during the preparation of vaginal rings. J. Pharm. Sci., 92: 258-265.
24. Zolac, S., M.Z.I. Khan, V. Gabelica, M. Tudja, Mestrovic., M. Romih, 1999. Paracetamol- propyphenazone interaction and formulation difficulties associated with eutectic formation in combination solid dosage forms. Chem. Pharm. Bull., 47: 302-307.