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A Review on Formulation and Characterization of Hydrochlorothiazide Solid Lipid Microparticles Based on Lipid Matrices of Irvingia Fat

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ABSTRACT

Hypertension is the most common modifiable risk factor for death and disability including stroke, accelerated and systemic atherosclerosis, heart failure, chronic kidney disease, lowering the BP with antihypertensive drugs, and lowering the incidence of cardiovascular disease and the damage to the target organs. The present review was about the solubilization, bioavailability and permeability of hydrochlorothiazide. This study explains about formulation and characterization of hydrochlorothiazide (HCTZ) solid lipid microparticles (SLM) utilizing *Irvingia* fat as the lipid matrix. Solid lipid microparticles have very good prospects as a good and an effective alternative to the traditional colloidal carrier systems like liposomes, emulsions and polymeric microparticles, for the encapsulation, targeting and controlled deliver of drugs and other activities. The microparticles endure prepared by using a hot homogenization method. The formulation parameters, including the lipid-to-drug ratio and surfactant concentration, were optimized to achieve desirable microparticles. Characterization of the microparticles involved evaluating particle size distribution, morphology using scanning electron microscopy (SEM), drug loading efficiency, encapsulation efficiency, invitro drug release kinetics. The physical stability of the microparticles was also assessed over time. High drug loading efficiency and encapsulation efficiency were achieved, indicating effective incorporation hydrochlorothiazide inside the lipid matrix. Invitro drug release studies revealed sustained release kinetics of hydrochlorothiazide from the microparticles over time. The physical stability studies demonstrated the stability of the microparticles under storage conditions. Overall, this review provides a comprehensive understanding of the formulation and characterization of hydrochlorothiazide solid lipid microparticles based on lipid matrices in *Irvingia* fat, highlighting their potential for controlled drug delivery application.

INTRODUCTION:

Hydrochlorothiazide is one of the best thiazide diuretic. It acts orally and the dosage form used for the usage of congestive heart failure and hypertension range from 25 to 50g daily alone or combination with other antihypertensive drugs up to 100mg if necessary. Hydrochlorothiazide has a half-life approximately 2.5 hours and oral bioavailability 70% [1]. It is only absorbed from the upper part of the duodenum and once it passes this absorption site, little or no absorption takes place [2].

Due to its great global incidence, hypertension is a serious public health issue [3-6]. High blood pressure is the cause of over 7.5 million fatalities worldwide each year, or 12.8% of all deaths [7]. It is anticipated that the number of adults with hypertension will rise to 1.56 billion [8]. It sounds like you are express a condition that often goes unnoticed until it reaches a critical state, such as heart attack, stroke, or chronic kidney disease. It is important to prioritize regular check-ups and screenings for early detection and prevention [9-11].

Currently, approximately 40% of the marketed immediate-free oral drugs are identified as practically insoluble (<100mg/ml) [12]. Lipid based formulations are typically reputed to improve the solubility and bioavailability of per orally administered poorly soluble drug [13]. Commonly, the solubility of an amorphous drug is higher than that of the equivalent crystalline drug. The difference in the solubility between amorphous form and crystalline form has been observed between 1.1- and 1000-fold [14]. By incorporation of poorly water-soluble drugs in the solid lipid matrix were led to improved bioavailability, protection of sensitive drug molecules from the outer environment (water, light) and even controlled release characteristics [15]. Solid lipid microparticles are usually [SLMs] are usually presented as emulsion systems, differing from conventional emulsions by their particulate nature and can be lyophilized in to discrete microparticles [16]. For improved functionality, the lipid matrices can be structured with phospholipids. The composition of the lipid matrix and this physical and chemical properties such as crystallization of the components are important for the drug loading capacity of nanoparticles and microparticles [17].

Irvingia gabonensis var. *excelsa* (*Irvingia wombolu*) is a tropical African tree. It contains fat in their seeds or nuts [18,19]. Fat extracted from the nut of this plant can be used for food, cosmetic and pharmaceutical applications [20]. Fat obtained from the nut of the plant is generally regarded as safe and has been consumed locally in Africa for centuries. Therefore, it would be ideal to look into how well it works in lipid-based drug delivery system.

Class IV of the classification system because to its poor permeability of membrane and low solubility in water. Consequently, HCTZ is, therefore, a good drug for advanced lipid formulation in order to achieve improved bioavailability which could lead to dose reduction and decreased side effects. In addition, reduced side effects of hydrochlorothiazide may promote patient compliance and eventually therapeutic performance of the formulation.

This review focus to study the efficacy and safety of hydrochlorothiazide from the formulation and characterization of hydrochlorothiazide solid lipid microparticles based on fat derived from *Irvingia* gabonensis var. excelsa (*irvingia* wombolu) and phospholipon® 90G (P90G).

Solid lipid microparticles (SLM)

Microparticles or microspheres, as they are interchangeably called,are fine spheres usually less than 1000um in diameter. Microparticulate can be preapred by well-established manufacturing processes. Adrug that has been integrated can either be uniformly dispersed throughtout the polymer martix (microparticles) or it can be encapsulated to create a drug resovoir (microcapsules) by enclosing it with polymer [21]. Solid lipd microparticles (SLM)are defined as solid lipid, approximately spherical particles ranging in size from 1 to 1000um. They are made of polymeric, wax or other protective materials, that is, biodegradable synthetic polymers and modified natural products such as starches, gum, proteins, plump and waxes. These micrometer-sized particles consist of a solid fat core based on naturally occuring lipid and stabilized by surfactant molecules[22].

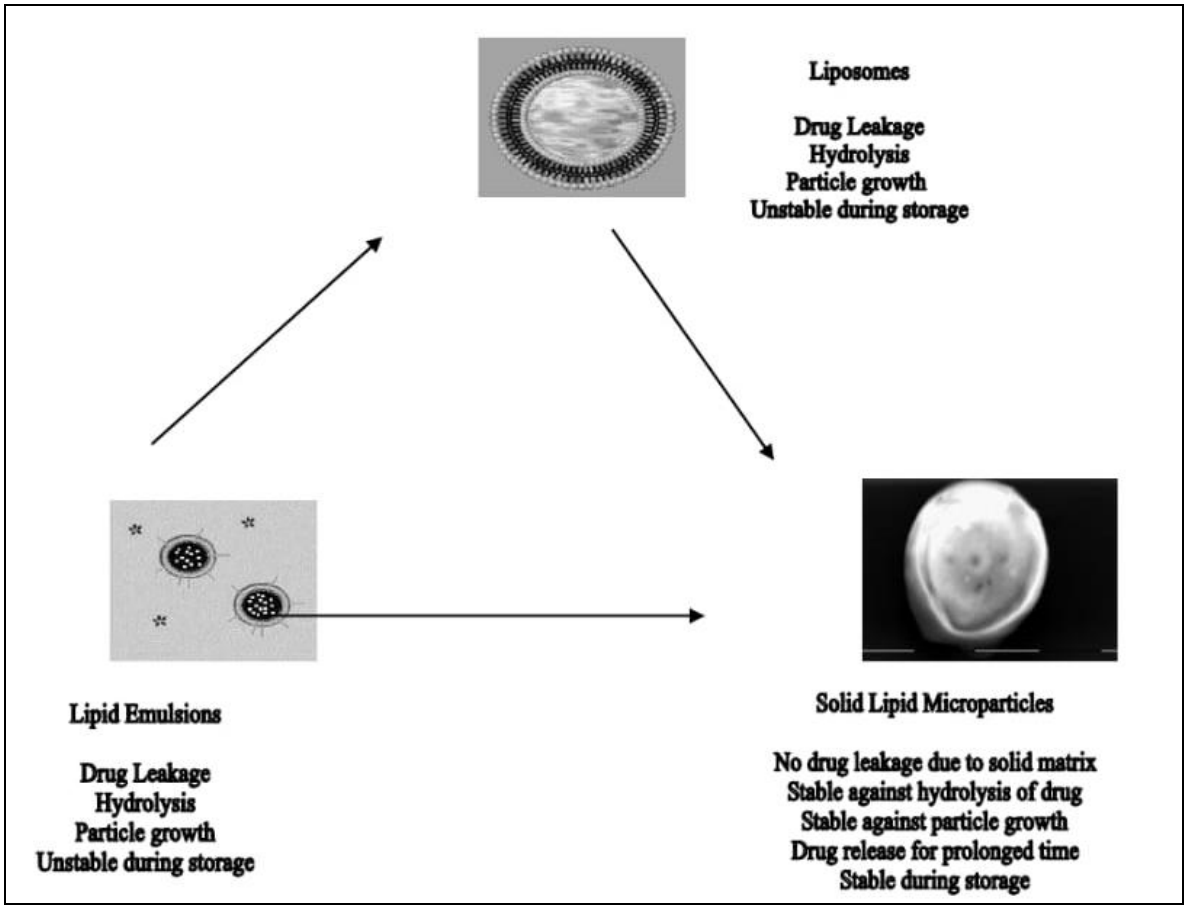

Figure 1.1: Different particulate organization applied in drug delivery with their characteristics.

- **Advantages of solid lipid microparticles (SLMs)**

1. High stability
2. Feasibility of scale-up
3. Reduced toxicity
4. Possibility of drug targeting and controlled release
5. Protection of incorporated labile medicament against chemical degradation
6. Use of biodegradable lipids
7. Allow water-attracted and /or hydrophobic antidote to be incorporate
8. For drug and carreir system, there is stability in both chemical and physical storage.

➢ **Clinical applications of solid lipid microparticles (SLMs)**

1. SLM have been as a carrier system for the delivery of drugs in the treatment of inflammatory bowel disorder using curcumin [23].

2. Budesonide loaded solid lipid microparticles have been demontrated to be of potential benefit in the teatment of pulmonary disease in vivo[24].

3. SLM have been determine to be effective as carrier for solid lipid nanoparticles (SLN) e.g. inhalable microparticles were used as carrier for the pulmonary delivery of thymopentin-loaded SLNs [25].

4. SLM are also employed in imaging e.g. imagent, a perflexane lipid microparticles is used in clinics or hospitals to determine gastrointestinal problems through magnetic resonance imaging (MRI). It is used to differentiate the problems from the normal structures. It effects the bowel contents, showing on the MRI image as a black spot[26].

5. Lipid microparticles of cosmetic factors such as glycolic acid have shown decreased irritation potential, while the fusion of quercetin in lipid microparticles improved photo and chemical stability of the flavinoid[27].

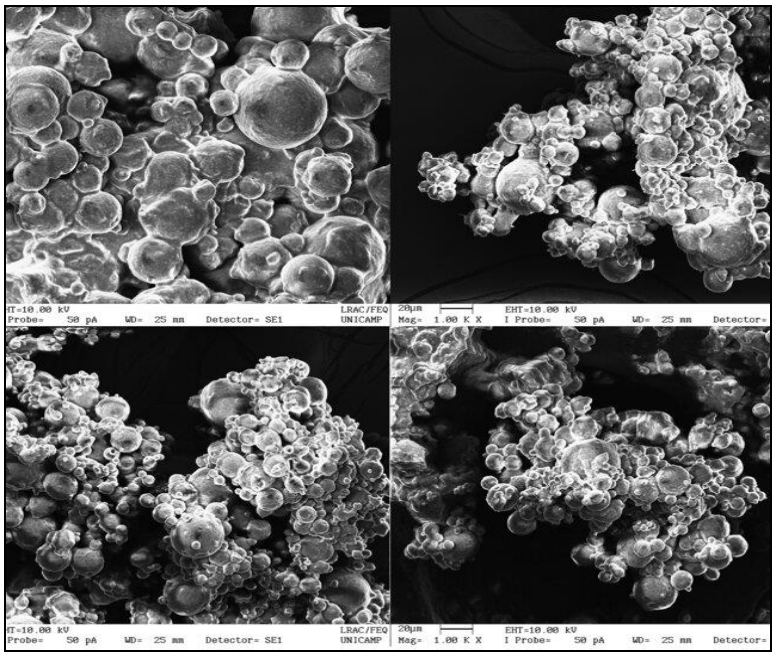

Figure 1.2 : Scanning electron microscopy of solid lipid microparticles

❖ MATERIALS AND METHODS:

➢ Materials

Phospholipon 90G (P90), hydrochlorothiazide, labrasol, *Irvingia* fat.

➢ Extraction of fat form

Irvingia gabonensis var. *excelsa* (*Irvingia wombolu*) from the nut of irvingia gabonensis var., fat was recoded. *excelsa* with petroleum ether (40 to 60^0C) using column extraction and concentrated with a rotary evaporator. The nuts were milled to course form and dried previous to start charcoal and bentonite in the lipid at 50^0C for 1hr. Following that, the suspension was vacuum-filtered Buchner funnel. The kind of fast in often referred to as "dika fat". The yield of extracted to extraction. Further purification was carried out by heating a 2%w/w suspension of a 1:9 ratio blend of *Irvingia* fat was calculated using equation.1:

$$\text{Yield\%} = [\text{weight of extracted } \textit{Irvingia} \text{ fat/weight of dried } \textit{Irvingia} \text{ nuts}] \times 100$$

❖ Formulation and optimization of unloaded solid lipid microparticles

Hot homogenization was used to produce solid lipid microparticles. *Irvingia* fat (5%w/w) was melted at 60^0C while aqueous labrasol® surfactant solution (1.5%w/w) was maintained at same temperature in an electronic thermostat water bath for 5min. Appropriate quantity of HCTZ. The surfactant solution was melt in the molten *Irvingia* fat to formulate SLM dispersions containing 1%w/w HCTZ. The melted irvingia fat laden with HCTZ was then gently stirred in the surfactant solution. The mixture was immersed in the water bath and homogenized at 20,000rmp for 5 minutes using an ultra-turrax® mixer. Subsequently the dispersion (HD SLM dispersion) was allowed to cool and subsequently stored in a refrigerator (4^0C). The procedure was repeated using *Irvingia* fat/P90G LMs at 3:1, 4:1, and 9:1 mass ratioes to form PDP3, PDP4 and PDP9 SLM dispersion respectively. The P90G was pre-heated at 80^0C prior to lipid fusion.

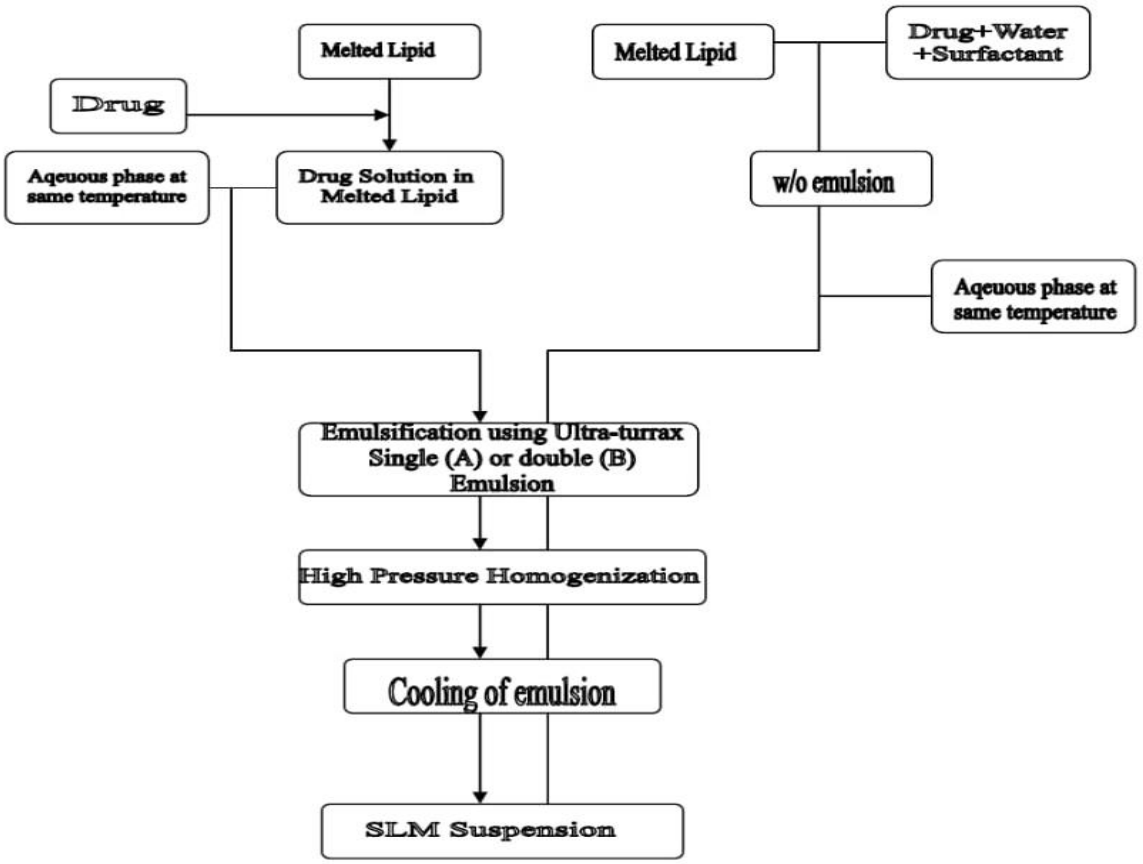

Figure 2.1 : Hot homogenization technique of solid lipid corpuscular preparation

❖ **Characterization of the solid lipid microparticles**

➢ **Particle size analysis, morphology, and polydispersity**

Using a motic ® digital light microscope to examine thin slide sample of dispersion and motic ® cameras to take and process image, motic ® image plus 2.0 software was used to study the particles size and morphology. The polydispersity index was calculated as the ratio of standard deviation to the mean particle size of the solid lipid microparticles. The pH of the dispersions was studied using a validated pH meter. The electrode part of the pH meter was immersed into 50ml quantities of each dispersion, and the reading was documented.

➢ **Drug encapsulation efficacy, drug loading capacity and yield (%)**

The content of hydrochlorothiazide in the microparticles was determined using UV spectrophotometric method the solid lipid microparticles dispersion was centrifuged at 3000rpm for 20min and the supernatant was analyzed with a UV-VIS spectrophotometer (spectrum lab 752s) at 273nm respectively after appropriate dilutions. A laboratory desktop

centrifuge (model SM 800B) was used for centrifugation. The drug encapsulation efficiency (EE%) of the loaded microparticles was calculated using equivalence 2 and 3.

EE% = [Real drug loading / Theoretical drug loading] ×100 [2]

$EE\% = W_{total} - W_{free} / W_{total} \times 100$ [3]

Where W_{total} = Weight of the drug added to the system

W_{free} = Weight of free drug dissolved in medium or supernatant

The drug loading capacity (DLC%) was calculated using Equivalence 4

$DLC\% = W_{total} - W_{free} / W_{total} - W_{free} + W_{lipid} \times 100$ [4]

Where the weight of lipid introduced to the system is denoted by W_{lipid}.

The percentage yield of the SLMs after the homogenization preparation process, was calculated using Equivalence 5

Yield% = [Actual weight of SLM / Theoretical weight of SLM] ×100 [5]

- **Syringeability**

The compositions` syringeability was evaluated by subjecting each dispersion to a variety of needle gauges of differing size (18G,21G,22G, and 23G). The syringeability of a sample formulation is determined by measuring the smallest needle gauge that the full sample can pass through.

- **Freeze-thaw cycle test**

The temperature of storage of the solid lipid corpuscular dispersions was varied between 4^0C, 25^0C, and 40^0C for one cycle. The physical stability and drug content the different formulations were evaluated after one week and one month.

- **Differential scanning calorimetry of lyophilized solid lipid microparticle dispersions**

A lyophilizer/ freeze dryer was used to lyophilize a suitable volume of every dispersion. This process converted the dispersions to powder. Differential scanning calorimetry (DSC) was then performed on samples of hydrochlorothiazide solid lipid microparticle dispersion using a DSC instrument at a temperature range of 30 to 400^0C and heating 10K/min rate on an

aluminum pan with a perforated top. The DSC of the SLM samples was used to assess their thermal property, and transparent and to observe any chemical interaction between components of the SLM.

- **Drug release and diffusion studies of solid lipid microparticle dispersions**

SLM dispersion in appropriate amounts equal to 25 mg of HCTZ were each encased in dialysis membrane tubing (molecular weight cutoff5000-8000) that had the same diameter and length (3cm) and width (2.5cm) for all the tests. The enclosed dispersion were submerged in 900ml of simulated gastric fluid in a beaker mounted on a magnetic stirrer assembly, and the medium was maintained at 37 ± 1^0C and stirred at 50 rpm. Using a spectrum lab 752s UV-VIS spectrophotometer, a series of 5 ml quantities of the solution were removed at 30 minutes intervals for six hours and then tested at 273 nm.

- **Kinetic and mechanism of drug release and diffusion**

The cumulative amount of HCTZ released from the formulated dispersion at different time interval were fitted to the following plots; zero-order kinetic model using cumulative percentage drug release versus time or "Q versus t"; [28] first order kinetic model using log cumulative of percentage drug remaining versus time or "Log (100-Q) versus t"; [29]. The drug release from a matrix system is described by the Higuchi model. It`s based on the square root of time, where the cumulative percentage drug release is proportional to the square root of time. Q versus $t^{1/2}$[30]. This relationship is often expressed as:

$$Q = k\sqrt{t}$$

Here, (Q) is the cumulative drug release at time (t), and (k) is a constant. The plot of cumulative percentage drug release versus the square root of time should ideally result in a linear relationship if the Higuchi model implement to the drug release from your system. The slope of the line in such a plot represents the (k) constant.

Statistical analysis

One-way analysis of variance was used to analyze the data. In data analysis, both descriptive and inferential statistic were used. $P < 0.05$ Was considered to be statistically significant.

Applications of Hydrochlorothiazide

1.Identify appropriate indications for Hydrochlorothiazide in treating hypertension and peripheral edema, considering patient-specific factors

2.Difference between hydrochlorothiazide and other thiazide-type diuretics, understanding their comparative effectives, adverse effects, and individual patient profiles.

3. utilize your understanding of the mechanism of action of hydrochlorothiazide to identify how they affect sodium resorption and how they cause natriuresis and diuresis.

4.Collaberate with other inter professional healthcare professionals to ensure comprehensive care and address any concern or complications related to hydrochlorothiazide therapy.

CONCLUSION:

The incorporation of hydrochlorothiazide in to solid lipid microparticles based on *Irvingia* fat and P90G modified the release of the hydrochlorothiazide drug and improved its permeability. This observation would possibly improve the bioavailability of the drug, allow for dose reduction and reduce associated side effects. It increases the excretion of sodium, water, potassium and hydrogen ions by blocking sodium reabsorption in the distal tubules. It is poorly water- soluble drug having plasma half -life 6-8 hrs. hence it is formulated in nanoformulations like solid lipid microparticles to enhance the absorbent and solubility of the drug. Solid lipid microparticles are more effective when compared to other nanoformulations. Lipid carriers have bright future due to their inherent property, SLMs constitute an attractive colloidal drug delivery system due to successful incorporation of drug and their related benefits. SLMs are economical patient-friendly equipment for administration of drugs by various routes.

REFERENCES

1.Hardman JG, Limbird LE and Gilman AG. The Pharmacological basis of therapeutics. New York, McGraw Hill; 2001: pp 774.
2. Ayres J, inventor; Oregon State University, assignee. Expandable gastric retention device. United States patent application US 10/778,917. 2004 Nov4.
3. Erem C, Hacihasanoglu A, Kocak M, Deger O, Topbas M. Prevalence of prehypertension and hypertension and associated risk factors among Turkish adults: Trabzon Hypertension Study. Journal of public health. 2009 Mar 1;31(1):47-58.
4. Ahmed A, Rahman M, Hasan R, Shima SA, Faruquee MH, Islam T, Haque SE. Hypertension and associated risk factors in some selected rural areas of Bangladesh. International journal of research in medical sciences. 2014 Jul;2(3):925.

5. Mishra C. P., Kumar S. Risk factors of hypertension in a rural area of Varanasi. *Indian Journal of Preventive and Social Medicine*. 2011;42(1):101–111.
6.Mishra CP, Kumar S. Risk factors of hypertension in a rural area of Varanasi. Indian J Prev Soc Med. 2011 Jan;42(1):101-1.
7.Mendis S, Armstrong T, Bettcher D, Branca F, Lauer J, Mace C. World Health Organisation; 2010. Global status report on noncommunicable diseases 2010. World Health Organization http://www. who. int/nmh/publications/ncd_ report2010/en. 2014.
8.Tabrizi JS, Sadeghi-Bazargani H, Farahbakhsh M, Nikniaz L, Nikniaz Z. Prevalence and associated factors of prehypertension and hypertension in Iranian population: The lifestyle promotion project (LPP). PloS one. 2016 Oct 26;11(10): e0165264.
9.Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo Jr JL, Jones DW, Materson BJ, Oparil S, Wright Jr JT, Roccella EJ. Seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure. hypertension. 2003 Dec 1;42(6):1206-52.
10 Botzer A, Grossman E, Moult J, Unger R. A system view and analysis of essential hypertension. Journal of hypertension. 2018 May 1;36(5):1094-103.
11. Prabakaran J, Vijayalakshmi N, VenkataRao E. Prevalence of hypertension among urban adult population (25-64 years) of Nellore, India. Int J Res Dev Health. 2013 Apr;1(2):42-9.
12. Takagi T, Ramachandran C, Bermejo M, Yamashita S, Yu LX, Amidon GL. A provisional biopharmaceutical classification of the top 200 oral drug products in the United States, Great Britain, Spain, and Japan. Molecular pharmaceutics. 2006 Dec 4;3(6):631-43.
13. Pouton CW. Lipid formulations for oral administration of drugs: non-emulsifying, self-emulsifying and 'self-microemulsifying'drug delivery systems. European journal of pharmaceutical sciences. 2000 Oct 1;11: S93-8.
14. Pouton CW. Lipid formulations for oral administration of drugs: non-emulsifying, self-emulsifying and 'self-microemulsifying'drug delivery systems. European journal of pharmaceutical sciences. 2000 Oct 1;11: S93-8.
15. RH M. Solid lipid nanoparticles (SLN)-an alternative colloidal carrier system for controlled drug delivery. Eur J Biopharm. 1995;41: 62-9.
16. Jaspart S, Bertholet P, Piel G, Dogné JM, Delattre L, Evrard B. Solid lipid microparticles as a sustained release system for pulmonary drug delivery. European journal of pharmaceutics and biopharmaceutics. 2007 Jan 1;65(1):47-56.
17. Schubert MA, Müller-Goymann CC. Characterisation of surface-modified solid lipid nanoparticles (SLN): influence of lecithin and nonionic emulsifier. European journal of pharmaceutics and biopharmaceutics. 2005 Sep 1;61(1-2):77-86.
18. Onyeike EN, Olungwe T, Uwakwe AA. Effect of heat-treatment and defatting on the proximate composition of some Nigerian local soup thickeners. Food chemistry. 1995 Jan 1;53(2):173-5.
19. Ejiofor MA, Onwubuke SN, Okafor JC. Developing improved methods of processing and utilization of kernels of Irvingia gabonensis (var. gabonensis and var. excelsa). International Tree Crops Journal. 1987 Jan 1;4(4):283-90.
20. Ejiofor MA, Onwubuke SN, Okafor JC. Developing improved methods of processing and utilization of kernels of Irvingia gabonensis (var. gabonensis and var. excelsa). International Tree Crops Journal. 1987 Jan 1;4(4):283-90.
21. Yang L, Alexandridis P. Physicochemical aspects of drug delivery and release from polymer-based colloids. Current opinion in colloid & interface science. 2000 Mar 1;5(1-2):132-43.
22. Dalpiaz A, Mezzena M, Scatturin A, Scalia S. Solid lipid microparticles for the stability enhancement of the polar drug N6-cyclopentyladenosine. International journal of pharmaceutics. 2008 May 1;355(1-2):81-6.
23. Yadav VR, Suresh S, Devi K, Yadav S. Novel formulation of solid lipid microparticles of curcumin for anti-angiogenic and anti-inflammatory activity for optimization of therapy of inflammatory bowel disease. Journal of Pharmacy and Pharmacology. 2009 Mar;61(3):311-21.
24. Mezzena M, Scalia S, Young PM, Traini D. Solid lipid budesonide microparticles for controlled release inhalation therapy. The AAPS journal. 2009 Dec; 11:771-8.

25. Drug Name: Imagent (Perflexane lipid microspheres), 2002 [cited 2012 June 10]. Available from: http://www.centerwatch.com/drug-information/fda-approvals/drugdetails.aspx?DrugID=786 Umeyor et. al., Am. J. PharmTech Res. 2012; 2(6) ISSN: 2249-3387 www.ajptr.com 18

26 Li YZ, Sun X, Gong T, Liu J, Zuo J, Zhang ZR. Inhalable microparticles as carriers for pulmonary delivery of thymopentin-loaded solid lipid nanoparticles. Pharmaceutical research. 2010 Sep;27: 1977-86.

27. Pol AN, Patravale VA. Novel lipidbased systems for improved topical delivery of antioxidants. Household and Personal Care Today. 2009;4(5).

28. Narashimhan B, Mallapragada SK, Peppas NA. Release kinetics, data interpretation. In: Mathiowitz E, editor. *Encyclopedia of Controlled Drug Delivery.* New York: John Wiley and Sons, Inc; 1999. p. 921.

29. Dash S, Murthy PN, Nath L, Chowdhury P. Kinetic modeling on drug release from controlled drug delivery systems. Acta Pol Pharm. 2010 May 1;67(3):217-23.

30. Higuchi T. Mechanism of sustained-action medication. Theoretical analysis of the rate of release of solid drugs dispersed in solid matrices. *J Pharm Sci.* 1963; 52:1145–9.