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DEVELOPMENT AND EVALUATION OF BILAYER TABLET CONTAINING RALOXIFENE HYDROCHLORIDE AND RISEDRONATE SODIUM FOR THE MANAGEMENT OF OSTEOPOROSIS

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Abstract: Osteoporosis, a systemic progressive disease, is responsible for significant morbidity and mortality in aging postmenopausal women. It is an important public health problem because of its significant complications, namely fractures of the proximal femur (hip), vertebrae (spine), distal forearm, proximal humerus, pelvis, and other skeletal sites. Compared with other osteoporotic fractures, hip fractures incur the greatest morbidity and direct medical costs for health services. There are now a variety of treatments available for the management of osteoporosis. Inhibitors of bone resorption, including calcium, vitamin Ds, bisphosphonates, calcitonins and gonadal steroids prevent bone loss or reduce fractures. Prevention of osteoporosis with identification of risk factors, careful examination and a few simple diagnostic tests during teen and early adult years is superior to treatment of older individuals. The purpose of this article is to provide a review of osteoporosis.

I. INTRODUCTION

The origin of the word 'osteoporosis' begins from the explanation of the condition - 'osteo' stands for bones, and 'porosis' means porous, resulting in weakness. [(1)]Osteoporosis is a common disease characterized by a widespread reduction in bone mineral density (BMD), micro-architectural deterioration. [(2)]Osteoporosis is one of the major public health problem associated with aging. Nowadays, it is defined as a skeletal disorder characterized by bone strength predisposing a person to an increased of fracture. There are two aspects which influences the bone strength, which is bone density and bone quality. Each standard deviation (SD) decrease in bone mineral density and the risk of fractures are correlated with each other.A BMD value between 1 and 2.5 SD below the mean value for young adults is considered as osteopenia condition. In consideration of BMD, osteoporosis is defined as BMD more than 2.5 standard deviations below the adult mean value. This classification originally has been proposed by the WHO in 1994 for the hip BMD of postmenopausal Caucasian women, but in clinical practices it is also used for men and for DXA measurements at the lumbar spine. [(3)] Osteopenia is a condition of bone that is slightly weaker and denser than normal bone but the pertinent bone condition is better than the degree of bone in osteoporosis.Normal bone is composed of protein, collagen, and calcium, all of which give strength to bone.In the case, when bones are affected by osteoporosis, it can break (fracture) with relatively minor injury from that of a normal bone that would not cause a bone to fracture. The fracture can be either in the form of cracking (as in a hip fracture) or collapsing (as in a compression fracture ofthe vertebrae of the spine). Although any skeleton bone can cause osteoporosis related fractures.

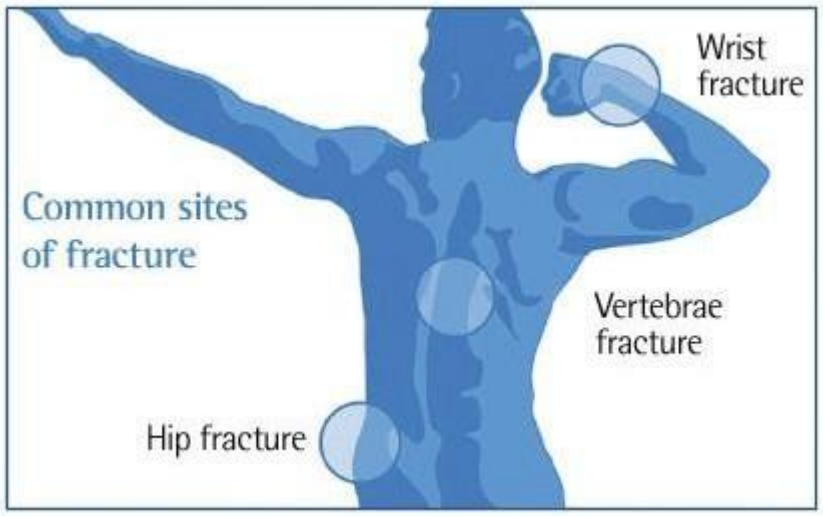


Figure no. 1: - Common sites of fracture

With osteoporosis, trivial slip-and-fall accidents can typically results as hip fractures. After surgical repair during hip fracture there may be slow or poor heal because of poor healing of the bone. [4]Most commonly, the two reasons due to which people tend to get osteoporosis can be because of low peak bone mass at the time of skeletal maturity, or accelerated bone loss at the time of menopause. At the time of skeletal maturity an individual obtain its highest bone mass, and loses bone steadily thereafter. Therefore, it is of extreme importance that by taking suitable measuresand related responsibilities young individuals should develop as healthier bone as possible.

Once loss in bone begins, it is also necessary to make sure that the rate of bone loss is slow. The amount of bone loss gets accelerated at the time of menopause. Some people take proper medications to prevent this bone loss. [5]Osteoporosis is characterized by low bone mass with micro architectural deterioration of bone tissue leading to enhanced bone fragility. This increases the susceptibility to fracture.Osteoporosis is a silent disease, reflected only in a low bone density, till a fracture occurs. Much in the manner that asymptomatic conditions such as hypertension and dyslipidaemia predispose

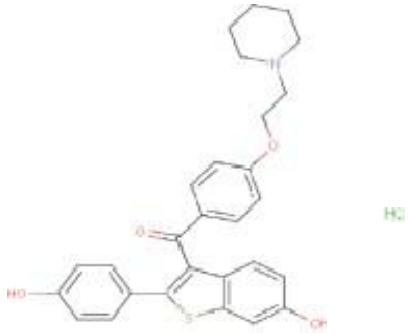
III.RESEARCH ENVISAGED

Osteoporosis is of particular interest to postmenopausal women, but the bone condition also affects other crowds of people.Despite continuing advances in osteoporosis detection and treatment alternatives, studies recommend that osteoporosis (a systemic skeletal disease leading to fracture, morbidity, andexcess mortality) continues to be poorly administered, undertreated, and under diagnosed. Between 5.2% to slightly more than 50% of women with fragility fractures are ever treated for osteoporosis. Fractures associated with osteoporosis (fragility fractures) have a major impact on quality of life, mortality, and health care costs.The boost in clinical information associated to osteopenia (a less severe level of bone loss) andosteoporosis has resulted in heightened awareness among health care professionals and the public that this critical issue must be addressed, and that current approaches to osteoporosis management must be improved.At certain, the incidence of low-impact, or fragility, fracture, and findings that many patients with fragility fracture are never tested or treated for osteoporosis, or when treated fail to persistin compliance with medication, improvement in care is a keystone of health care‟s humanitarian mission.So, to get advanced management of osteoporosis with improved patient‟s compliance we recommended the combination therapy including two categories of drugs used for themanagement of osteoporosis that is Raloxifene Hydrochloride (immediate release) and Risedronate sodium (sustained release) as a bi-layer tablet.

IIII. DRUG PROFILE

Raloxifene Hydrochloride [53, 54]

Chemical structure:



Molecular Formula: $C_{28}H_{27}NO_4S \cdot HCl$

Molecular Weight: 510.05

IUPAC Name: Methanone, [6-hydroxy-2-(4-hydroxyphenyl) benzo [*b*]thien-3-yl]-[4-[2-(1-piperidinyl) ethoxy] phenyl]-, hydrochloride

Category: selective estrogen receptor modulator (SERM) \

Dosage and Administration:

Adult women: PO 60 mg every day.

Description: off-white to pale-yellow solid

Solubility: very slightly soluble in water.

Storage/Stability: Store at 59° to 86°F.

IV. PLAN OF WORK

Preformulation studies

Physical appearance
Melting point
Solubility studies
Partition coefficient

V.EXPERIMENTAL WORK

Preformulation testing is defined as investigation of physical and chemical properties of a drug substance alone and when combined with excipients. The overall objective of preformulation testing is to generate information useful to the formulator in developing stable and bioavailable dosage form that can be mass produced. Before beginning the formal preformulation programs the preformulation scientist.The amount of drug available.The physicochemical properties of the drug already known. Therapeutic category and anticipated dose of compound.

The Melting point was determined by the capillary method using Melting point apparatus. Here,the capillary tube was filled by pressing the open end gently into Risedronate sodium and Raloxifene hydrochloride (pure drug) sample by tapping the bottom of the capillary on a hard surface so that the drug pack down into the bottom of the tube. When the drug was packed intothe bottom of the tube, the tube placed into the slot behind the eye-piece on the Melt-temperature. The unit was plugged in and set to zero and then turned it on and near its reporting melting point, the temperature increased slowly.

The solubility of drugs were an important physicochemical property because it affects the bioavailability of the drug, the rate of drug release into dissolution medium and consequently, the therapeutic efficiency of the pharmaceutical product. The solubility of the molecules in various solvents was determined as a first step. This information is valuable in developing a formulation. Solubility is usually determined in variety of commonly used solvents and some oils if the molecule is lipophilic. The solubility of material is usually determined by the equilibrium

Partition Coefficient (oil/ water) is a measure of a drug‟s lipophilicity and an indication of its ability to cross cell membranes. It is defined as the ratio of unionized drug distributed betweenthe organic and aqueous phases at equilibrium.

P o/w = (C oil / C water) equilibrium.

For series of compounds, the partition coefficient can provide an empiric handle in screening for some biologic properties. For drug delivery, the lipophilic/hydrophilic balance has been shown to be a contributing factor for the rate and extent of drug absorption. Although partition coefficient data alone does not provide understanding of in vivo absorption, it does provide a means of characterizing the lipophilic/ hydrophilic nature of the drug.

Formulations of Immediate release and Sustained release layer of immediate release layer

Ingredients	**IR_1**	**IR_2**	**IR_3**	**IR_4**	**IR_5**	**IR_6**	**IR_7**	**IR_8**	**IR_9**
Raloxifene hydrochloride	60	60	60	60	60	60	60	60	
Crosspovidone	7.5	3.25	10.75	-	-	-	-	-	-
Crosscarmellose sodium	-	-	-	7.5	3.25	10.75	-	-	-
Sodium starch glycolate	-	-	-	-	-	-	7.5	3.25	10.25
Span-80	5	5	5	5	5	5	5	5	5
Magnesium stearate	5	5	5	5	5	5	5	5	5
Talc	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Lactose	70	74.25	66.75	70	74.25	66.75	70	74.25	66.75
Isopropyl alcohol	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Total	**150**	**150**	**150**	**150**	**150**	**150**	**150**	**150**	**150**

All the amounts are shown as milligrams (mg).

VI.RESULTS AND DISCUSSION

Physical appearance

Physical appearance of Raloxifene hydrochloride

S.No	Parameters	Sample
1	Colour	Yellowish White
2	Odour	Odourless

Physical appearance of Risedronate sodium

S.No	Parameters	Sample
1	Colour	White
2	Odour	Odourless

The sample of Raloxifene hydrochloride and Risedronate sodium were identified as of whitecolour and odourless which were found to be as that of standard parameters.The aim of present study was to formulate and evaluate bi-layer tablet for management of osteoporosis which consist of Raloxifene HCl as immediate release layer and Risedronate sodium as sustain release layer. The combination of different pharmacodynamic profiles of drugs was used having no interaction at molecular level.In preformulation part, the FTIR studies were carried out to check possible interaction betweenthe drugs and the excipients and the study confirmed that there was no interaction between the selected drugs and excipients.

The Immediate release layer prepared by wet granulation method using sodium starch glycolate, cross povidone, cross carmellose sodium, talc, magnesium separate, isopropyl alcohol, span-80. The sustained release layer prepared by wet granulation method using HPMC E50, HPMC-E15, PVP, microcrystalline cellulose, talc, magnesium stearate and isopropyl alcohol. Both the layers were separately optimized and prepared. The granules of both the layers were evaluated for angle of repose, bulk density, tapped density, ratio and Carr‟s index. The angle of repose shows that powder for all batches had good flow ability except IR_4, IR_6, IR_8 in immediate release and SR_6 in sustain release. The compressed tablet was evaluated for its hardness, weight variation and friability.

The In-vitro release study was carried out of all the batches of sustained release using veego USP dissolution apparatus. The drug release of the drugs depends on HPMC E50 and HPMC-15 for sustained release. In sustained release SR_2 and SR_4 shows highest amount of drug release and most effective IR_3 and IR_9 in immediate release. So IR_3 and IR_9 of immediate release and $SR_2$and SR_4 of sustained release were found to be optimized batches. The sustained release layer shows 98.93% release in 12hrs (SR_2) and 99.93% release in 12hrs in (SR_4). The optimizedsustain release tablets shows better drug release pattern than marketed preparation. The Bi-layer tablets of optimized batches were prepared and in-vitro drug release was determined

VII. ACKNOWLEDGMENT

In order to excel, you must be completely dedicated to your chosen field. You must also be prepared to work hard and be willing to accept new changes and developments. Without 100% dedication, you won't be able to do this."This report has been kept on track and been seen through to completion with the support and encouragement of numerous people including my well-wishers, my friends, colleagues. I would like to thank all those people who made this report possible and an unforgettable experience for me. I express my thanks to all those who contributed in many ways to the success of this study and made it an unforgettable experience for me.

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