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Formulation and Evaluation of Controlled Release Tablet Using Thyme and Rosemary for Osteoporosis

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Abstract:- Osteoporosis is a common public health problem which currently affected millions of people worldwide. Osteoporosis is mainly associated with Ovarian hormone deficiency following menopause is till now a most common reason of age-related bone loss. There are tablets that are available in the market, which shows the side effect such as nausea, heart burn, gastric problem after the continuous use of medicine. These side effects led to the avoidance of such medicine. Using herbal plant such as thyme and rosemary as an alternative of those drug will help to reduce these effects. Hence, selected to develop a Controlled Release Tablet of Rosemary and Thyme. Tablet is the most popular among all dosage forms existing today because of its convenience of self-administration, compactness and easy manufacturing. Developing the tablet using thyme and rosemary in the form of controlled release drug will help to prolonged the effect of the medicine. As precision of dosing, to improve the bioavailability of the drug and to maintain the constant level of drug in the plasma become important to provide the long-term effect to the patient. It will also provide the patience compliance as well as prolonged the effect of drug in the patient's body.

Keywords:- *Osteoporosis, Controlled-Release Tablets, Rosemary, Thyme And Dosage Forms.*

I. INTRODUCTION

As the most common cause of age-related bone loss, osteo is mostly associated with the decrease in ovarian hormones that occurs after menopause. Osteoporosis is a "silent" ailment since it seldom causes noticeable symptoms; as a result, it often goes undetected until a bone breaks.[1] Fractures in older adults, particularly those who have gone through menopause, are most commonly caused by osteoporosis. Fractures can happen to any bone, but the most common ones are the vertebrae in the spine, hips, and wrists. Osteoporosis affects men and women of all races and ethnicities. Osteoporosis is more common in older people, however it may affect anybody at any age. In women, the symptoms usually appear around the time of menopause.[2,3] Osteoporosis is called a "silent" condition because it is often not detected until a bone breaks. Spinal abnormalities (kyphosis, for example), severe back pain, or a diminished stature.[4,5] Bones impacted by osteoporosis might weaken to the point that they break easily.[6] Osteoporosis occurs when there is an abnormal decrease in bone mass and subsequent structural abnormalities in bone tissue.[7] Certain risk factors can either cause osteoporosis to develop or increase the likelihood that the condition will develop. Many people who get osteoporosis have more than one risk factor, while some people may not have any at all. Bisphosphonates are the most popular drugs used to treat osteoporosis.[8] Bisphosphonates are useful in halting the loss of bone mass. Oral or intravenous administration is possible.[7]

A. Pathophysiology of Osteoporosis:

Loss of bone density, strength, mass, and quality characterizes osteoporosis. This condition develops when there are problems with bone remodeling, which causes mesenchymal stem cells (MSCs) to age and change their differentiation potential to prefer adipogenesis over osteogenesis.[9] As a result of this disease, bones become increasingly brittle and structurally compromised. The imbalance is primarily caused by differences in the activity levels of osteoblasts and osteoclasts. Two main types of osteoporosis may be distinguished: primary and secondary. There is no known medical condition that might trigger primary osteoporosis. Primary osteoporosis can be further classified into idiopathic and involutional forms. Children and young adults are most commonly impacted by idiopathic osteoporosis, the cause of which is unclear. Involutional osteoporosis, which can strike either sex, is mostly caused by age and hormonal abnormalities. Involutional osteoporosis is further subdivided into Type I and Type II. Type I, commonly called "postmenopausal osteoporosis," mostly impacts women who have gone through menopause. Rapid bone loss is a symptom of this disorder, which strikes women between the ages of 51 and 71.[10,11] Type II involutional osteoporosis, often known as "senile osteoporosis," affects most persons over the age of 75 and is characterized by trabecular and cortical bone loss. Fewer than five percent of osteoporosis cases are secondary, meaning they are caused by another medical condition or medication. It has long been recognized that the decrease in estrogen levels during menopause is one of the primary causes hastening bone loss.[12]

B. Dosage Form

Dosage forms, also known as unit doses, are pharmaceutical medication products in their prescribed form. These products include a specified combination of active and inert chemicals, as well as excipients, and are presented in a

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certain shape, such as a capsule shell. The term "drug delivery" describes the method of administering medication to a patient in such a way that some areas of the body receive a higher concentration of the drug than other areas.[13] The eventual goal of any delivery method is to safely target, limit, and prolong the drug in the diseased tissue. Various routes can be utilized to provide different dose forms, depending on factors such as the target location, duration of therapy, and the physicochemical qualities of the pharmaceutical. Needles, ointments, syrups, pills, capsules, and tablets are the most common modes of administration. When deciding how to deliver a medicine, it is important to consider the region that has to be treated, the drug's mechanism of action within the body, and the drug's solubility and permeability. Tablets are solid, unit dosage forms that include pharmacological substances with or without suitable diluents and are formed by molding or compression.[14] The active medicinal component and any excipients should be combined in a tablet using compression and molding procedures. Several viable approaches to the production of these pills have been identified. There are two different kinds of tablets: compressible and mouldable. a water-soluble tablet made of moldable, freeze-dried components that dissolve rapidly in saliva. But it's not easy to hold the tablet because its construction is so delicate. Making compressed pills is usually not costly.[14,15]

C. Controlled Release Tablet

Novel drug delivery methods include controlled-release dosage forms, which prolong drug release and keep the medication's plasma level constant. This is the method of medication administration that keeps the drug concentration in the blood and tissues constant for a long time. One dosage of a controlled medicine delivered by a particular formulation or technology demonstrates zero-order PK in the controlled delivery system. Within the therapeutic window, the medication levels are consistently maintained.[15,16]

D. Classification of Controlled-Release Tablets

Controlled-release tablets can be classified into mainly two parts Membrane-controlled and Matrix systems. In membrane-controlled systems, a thin polymeric membrane surrounds the core, which serves as a reservoir for the medication. The membrane may or may not have pores. The rate of drug release is determined by the physicochemical properties of the drug, which include its partition coefficient, molecular size, diffusivity, protein binding, and dose, as well as the membrane's thickness and porosity. For membrane-controlled reservoir systems, encapsulation and press coating of tablets are common fabrication procedures.The medication is either dissolved or uniformly distributed within the polymer matrix in matrix-controlled delivery systems. Drugs are released from the matrix by diffusion when the outer layer that is exposed to the solution dissolves first. Substantially below their solubility limit, medicines are put into matrix systems for dissolution.[17] The amount of medication discharged drops as the matrix size drops. The medication is released in a non-zero order here, meaning the rate of absorption is greater than the rate of excretion. The solubility limit is exceeded in matrix systems when the pharmaceuticals are spread in a polymer matrix.[18]

II. MATERIAL AND METHOD

Table 1: List of materials

MATERIAL	PROCURED FORM
Thyme	Plant
Rosemary	Plant
HPMC	Hi Media Laboratories PVT. LTD.
Lactose Monohydrate	Hi Media Laboratories PVT.LTD.
Talc	Merck Specialities PVT. LTD.
Magnesium Stearate	Loba Chemi PVT. LTD.
Iso Propyl Alcohol (IPA)	Thermo Electron LLS India PVT. LTD.

III. DRUG PROFILE

A. Thyme (Thymus Vulgaris)

Thyme is a herb that grows low, with little green leaves, and has a strong, fragrant scent. The Lamiaceae family counts it among its original inhabitants of the Mediterranean. The anti-inflammatory, antibacterial, and antimicrobial qualities of thyme are due in part to the essential oils it contains, such as thymol, carvacrol, and linalool. The medicinal properties of thyme include antimicrobial, antioxidant, and anti-inflammatory effects.[19] Thyme has a long history of use in herbal remedies for respiratory conditions and is known for its antimicrobial properties. It contains compounds with antioxidant properties that may help protect cells from oxidative damage. Research has shown that thyme and its extracts can reduce inflammation. Additionally, thyme aids in reducing inflammation in osteoporosis, according to many research. Soups, stews, and roasted meats are just a few of the many meals that benefit from the aromatic flavor of thyme, a beloved herb in the kitchen. Research on the anti-inflammatory and antibacterial properties of thyme has focused on its possible application in osteoporosis and respiratory disorders.[20]

B. Rosemary (Rosmarinus Officinalis)

An evergreen plant, rosemary has needle-like leaves and a strong scent. Also hailing from the Mediterranean, it is a Lamiaceae relative. Cineole, camphor, and rosmarinic acid are some of the essential oils found in rosemary.[21] Among its many health benefits, rosemary is known for its antioxidant capabilities, which may shield cells from free radical damage. Other research suggests that rosemary may also have anti-inflammatory effects. Roasted meats, veggies, and soups are common ways that rosemary is seasoned in Mediterranean cooking.[22]

C. Potential Health Benefits

Although further research is required to validate these advantages, rosemary has been investigated for its possible cognitive and memory-enhancing properties. Although thyme and rosemary have a long history of medicinal usage, people should not use them in place of professional medical care; rather, they should talk to their doctors about any particular health issues they may be experiencing. People

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who are pregnant or have specific medical concerns should also be cautious and see a doctor before taking herbal treatments.[23]

IV. EXCIPIENT PROFILE

Covalently bonded monomers form chains in excipients and polymers. They play an important role as medication carriers in oral drug delivery systems and are utilized extensively in the pharmaceutical sector. Controlled release formulations rely on polymers for structural support. To manage and maintain the matrix's stiffness over a lengthy period, polymers used in controlled release formulations must have particular qualities.[23,34]

Table 2: Examples of a Few Polymers used in Formulation of Controlled Release Dosage Forms

Hydrophilic Polymers	**Hydroxypropyl methylcellulose (HPMC), Methylcellulose, Hydroxypropyl cellulose (HPC).**
Non-Cellulosic	Xanthan Gum, Chitosan, Guar Gum.
Hydrophobic Polymers	Ethyl cellulose, cellulose acetate, Hypromellose acetate succinate.

A. Hydroxy Propyl Methyl Cellulose

Hypermellose is another name for it. 2-Hydroxypropyl ether (9004-65-3) is the CAS Registry Number and Chemical Name. It has a molecular weight of 1261.4 g/mol and an empirical formula of C56H108O30. A bioinspired polymer made from cellulose, hydrophobic propylene carbonate (HPC) is a nontoxic, odourless, yellowish powder that dissolves in water. 225–230°C was its melting point.[25,26] Emulsifying, stabilizing, thickening, and gelling are some of its many uses. Coatings made from this basic material have moderate strength, flexibility, clarity, and fat and grease resistance. Keep HPMC in its original container in a cold, dry, and well-ventilated area. Since it is a non-ionic cellulose ether derivative, HPMC is stable over the pH range of 3.0 to 11. To put it simply, HPMC is a semi-synthetic polymer.[27] Its strong mechanism for regulated drug release and variety of viscosity grades make it the material of choice for creating hydrophilic matrix systems. Because it is not ionic, it offers predictable release profiles and has few interaction issues in acidic, basic, or electrolytic environments. Additionally, it saves money. The pH of the fluid has no effect on HPMC matrices. Because of their great tensile strength, grades K4M and K100M are determined to be the most suitable for controlled release compositions.[28] The polymer chains detangle from the matrix when it is moistened. The rate of media penetration and matrix erosion control HPMC matrix systems, which are categorized as swelling controlled systems.[29] The presence of distinct fronts inside the matrix is determined by the rate of swelling in hydrophilic polymers. When the movement of these fronts is synchronized, the drug release rate remains constant.[30]

HPMC is a mixture of alkyl hydroxyalkyl cellulose ether containing methoxy and hydroxypropyl groups. The rate of hydration of HPMC depends on the nature of the substituent's that form the polymer e.g. molecular structure, degree of substitution.

Table 3: Various Grades of HPMC (taken from The Dow Chemical Company 2000)

HPMC type	**Methoxy (%)**	**Hydroxypropoxy**	**Other names**
K	19-24	4-12	Hypromelose2208
E	28-30	7-12	Hypromelose2910
F	27-30	4-7.5	Hypromelose2906

B. Lactose

Lactulose is a kind of sugar that comes from milk. The scientific and CAS names for this compound are 64-42-3 is the formula for β-D-galactopyranosyl-(1→4)-D-glucose. It has a molecular weight of 342.2965 g/mol and an empirical formula of C12H22O11. The galactose monomer in lactose forms a disaccharide that binds to glucose. A bit sweet in flavor, this solid is white, soluble in water, and non-hygroscopic. Due to its low price and bland flavor, lactose is a popular and inexpensive sweetener.[31] As a binder and filler, lactose has several potential applications. When it comes to pharmaceutical excipients, lactose is among the most stable options. Keep it in a room at room temperature. Lactose consists of two sugar molecules, galactose and glucose, joined together to form a disaccharide. Because of its remarkable compressibility, lactose finds widespread application in the pharmaceutical sector as an ingredient in tablet production. In addition to its use as a binder, bulking agent, and filler in medicinal formulations, lactose has other potential uses. Aside from being a cheap and readily accessible excipient in a variety of forms, it is also quite safe to use.[32,33]

C. Talc

Soapstone, Agalite, Mussolinite, and Asbestine are some of its alternate names. Hydrous magnesium silicate, with the CAS registry number 14807-96-6, is its chemical name. Its empirical equation is has a molecular weight of 379.27 g/mol and the formula Mg3Si4O10(OH)2. Magnesium, silicon, oxygen, and hydrogen make up the mineral talc, which is found in nature. It comes from the ground. A white-gray powder, talc has no discernible smell. To enhance the flow characteristics of powder, talc is often employed as a glidant. The medicinal preparation also makes use of it as a thickening agent and lubricant. Store in a cool, dry, and airy location, away from direct sunlight.[33] The

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container should be sealed firmly. Keep in the original packaging for future reference. Keep away from moisture. The pharmaceutical sector relies on talc, which is mined from pristine talc ores. India, the US, and China are the three countries that produce the most talc. Despite the lack of a chemical link between the silicate layers, they are kept together by weak Van der Waals forces, allowing them to readily slide past one other. Because of its physiochemical inertness, low cost, and wide range of dosage forms (tablets, capsules, pills, etc.), talc has been utilized as an excipient for a long time. Cosmetic preparations often include talc for its abrasive, bulking, anti-caking, absorbent, slip-modifying, and skin-protecting properties, while the pharmaceutical business uses it as an excipient for glidant, filler, and lubricant.[34]

D. Magnesium Stearate

Another name for it is magnesium salt of stearic acid. Magnesium octadecenoate, fatty acid C16–C18 magnesium salts, or magnesium di stearate is its chemical name and CAS registry number. No. 557-04-0. It has a molecular weight of 591.27 g/mol and an empirical formula of Mg(C18H35O2)2. You can think of it as a white, insoluble powder. One of its many uses is as an emulsifier, thickening, lubricant, and binder. As a flow agent, magnesium stearate is useful. It aids in preventing the components from dispersing. The formulation's quality is also enhanced. If kept in a properly sealed container in a cold, dry, and well-ventilated area, it will not spoil.[34] There is a 24- 36 month shelf life for magnesium stearate. The metallic salt boundary lubricant magnesium stearate is composed of two charged magnesium ions and one fatty acid molecule. It is widely utilized in many applications. An pricey lubricant with a high melting point and chemical stability, magnesium stearate is also very useful. The formulation was developed using a magnesium stearate concentration ranging from 0.25–5.0% w/w. Cosmetics and topical medical devices also make use of magnesium stearate to improve their water-repellent qualities. Concentrations ranging from 0.25 to 5% by weight are considered typical.[35]

V. IDENTIFICATION OF DRUG

A. Pre-Formulation Studies

Descriptive language was used to capture the drug's color, smell, and taste. The melting point may be found using a capillary tube. An understanding of a drug's solubility properties in water is crucial. Because in order to provide a therapeutic effect, they need to have a certain level of solubility in water. Several descriptive terms from the Indian Pharmacopoeia, 2018 were used to document the drug's solubility. Through the use of the fixed funnel method, the angle of repose was determined. A paper surface was set on a stand and positioned at a specific height above a vertically mounted funnel. The funnel was sealed at the base and then filled with powder. The powder was then spread out over the paper in a smooth conical mound once the funnel was opened. A formula was used to determine the angle of repose based on the measured height and radius of the heap.[36]

$\tan \theta = h/r$,
$\theta = \tan^{-1} h/r$

Where, θ = Angle of repose, h = Height of heap and r = radius

Table 4: Relationship between Angle of Repose (θ) and Flow Properties

Flow Ability	Angle of Repose
Excellent	<25
Good	25-30
Passable	30-40
Poor	>40

B. Bulk Density

A powder's bulk density is defined as the mass to volume ratio of an untouched sample of powder, taking into account the volume of inter-particulate voids. So, the bulk density is dependent on the particle density as well as the particle configuration in the powder bed. Although kilograms per cubic meter is the international unit of measurement, the bulk density is represented in milliliters per gram (g/mL).[37]

- **Bulk Density = m/Vo**, Where, m = mass of power, Vo = volume of the measuring cylinder.

C. Tapped Density

Once the initial powder volume or mass has been noted, the measuring cylinder or vessel is mechanically tapped to obtain readings of volume or mass until there is little further change. The cylinder or jar is raised and then let to fall, under its own weight, to accomplish the mechanical tapping. The ultimate volume was determined by tapping the cylinder at a rate of 15 taps per minute. When the original volume (Va) is equal to the end volume (Vb), the tapped density is only Va/Vb.[38]

D. Carr's Index

The Carr's index is an indicator of the compressibility of a powder. It is named after the scientist Ralph J. Carr, Jr. **Carr's index = (ρ tapped – ρ bulk)/ρ tapped*100.**

Table 5: Practical Consideration of Compressibility Index

% COMPRESSIBILITY INDEX	FLOW
5-15	Excellent
12-16	Good
18-21	Fair to Passable
23-35	Poor
33-38	Very Poor
>40	Very Very Poor

E. Hausner's Ratio

Hausner's ratio is a no. that measures the flowability of a powder or granular material. **Hausner's Ratio = ρ tapped/ρ bulk**

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Table 6: Practical Consideration of Hausner's Ratio

HAUSNER'S RATIO	FLOW
<1.25	Good
>1.25	Poor
1.25-1.5	Very Poor

VI. ANALYTICAL METHOD

A. *UV-Spectroscopy*

The analytical tool known as a UV-vis spectrophotometer can determine how much visible and ultraviolet (UV) light a sample absorbs. Identifying and quantifying molecules in a range of samples is a common practice in many scientific disciplines, including chemistry and biochemistry. UV-vis spectrophotometers measure the sample's absorption of light at different wavelengths by sending a light beam across it. A sample's light-absorbing capacity is directly related to its absorbing component content. The study was conducted using a spectra management software-equipped double beam UV-visible spectrometer (UV-730, Jasco). For the purpose of spectral measurement, quartz cells measuring 3 cm in length and 1 cm in path length were employed.[39]

- **Preparation of Phosphate Buffer (pH 6.8):** To make 1000 milliliters of phosphate buffer (pH 6.8), dissolve 13,872 grams of potassium dihydrogen phosphate and 35,084 grams of sodium hydrogen phosphate in enough distilled water.
- **Preparation of standard stock solution:** To make the standard stock solution, measure out 10 milligrams of thymol precisely. Fill a 100 ml volumetric flask with phosphate buffer (pH 6.8) and dissolve the thymol entirely, as shown in Stock 1. Solutions with concentrations of 2, 4, 6, and 8 ug/ml were generated by diluting stock 1 in a series of steps. Thoroughly measure out 10 milligrams of rosmarinic acid. Before dissolving the rosmarinic acid entirely in the phosphate buffer (pH 6.8), transfer it to a 100 ml volumetric flask [Stock 1]. The solutions with concentrations of 2, 4, 6, and 8 ug/ml were generated by diluting the stock 1 solution in a series of steps.
- **Determination of wavelength of maximum absorbance (λ max):** Fill the cuvette with the thymol standard solutions sequentially and measure their absorbance at 274nm to determine the wavelength of maximum absorbance (λ max). For every concentration, make a note of the absorbance readings. To measure the absorbance at 328 nm, fill the cuvette with a different standard solution of rosmarinic acid one at a time. For every concentration, make a note of the absorbance readings.
- **Preparation of calibration curve:** In Microsoft Excel 2016, we will plot the calibration curves that show concentration vs. absorbance. The purpose of repeatedly mentioning the approach was to ensure that reproducible outcomes could be achieved.

B. *Formulation*

Formulation of controlled release tablet using thyme and rosemary is done by using wet granulation method by direct compression.[40]

Table 7: Manufacturing formula of Thyme and Rosemary CRT (mg/ml)

Sr. No.	Ingredients	F1	F2	F3	F4	F5	F6
1.	Thyme	70	70	70	70	70	70
2.	Rosemary	400	400	400	400	400	400
3.	HPMC	32.5	48.75	65	81.25	97.25	113.75
4.	Lactose	134.5	118.25	102	85.75	69.5	53.25
4.	Magnesium Stearate	6.5	6.5	6.5	6.5	6.5	6.5
5.	Talc	6.5	6.5	6.5	6.5	6.5	6.5
6.	I.P.A.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.
TOTAL		650	650	650	650	650	650

VII. PROCEDURE

The API (Rosemary- 400mg, Thyme- 70mg), polymer (HPMC- 5%, 7.5%, 10%, 12.5%, 15% and 17.5%) and lactose was passed through 60# mesh. Then the drug, polymer and lactose were mixed uniformly and granulated with IPA (Iso propyl alcohol) by using wet granulation method. Then these granules were dried in a Hot air Over at 60oC.After drying the granules, they were uniformly blended with talc (1% w/w) and magnesium stearate (1% w/w). After blending the powder is punched in a tablet punching machine using 13-mm standard concave punches. Compression force on the release rate, was kept at a constant level required to produce tablet of about 6.0-kp hardness.

A. *Weight Variation*

The weight variation test would be a satisfactory method of determining the drug content uniformity. I.P. procedure for uniformity of weight was followed, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight.

Table 8: Specification as per IP

Average Weight of Tablet	% Deviation
80 mg or less	±10
More than 80 mg but less than 250 mg	±7.5
250 mg or more	±5

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B. Hardness

The hardness test, also known as tablet hardness or tablet breaking strength test, is a quality control measure done in the pharmaceutical industry to analyze the mechanical strength of tablets. This test helps guarantee that tablets can resist handling, packing, and transportation without breaking or disintegrating. Hardness tester is an apparatus which is used for hardness testing of the tablet.[33]

C. Friability

The friability test is a quality control measure used to assess the durability or resistance to abrasion of tablet formulations. It is a critical test in the pharmaceutical business to guarantee that tablets can resist handling, packing, and transportation without severe breaking or damage. The test is particularly significant for uncoated tablets. Calculate the % friability using the formula:

$$\text{Friability (\%)} = \frac{(\text{Initial Weight} - \text{Final weight}) \times 100}{\text{Initial weight}}$$

D. Content Uniformity

Content homogeneity is an important quality factor for pharmaceutical goods, guaranteeing that each dosage unit within a batch includes the same quantity of active pharmaceutical ingredient (API). It is particularly critical for drugs with a limited therapeutic range, because tiny adjustments in dose can have a large influence on efficacy and safety.[40]

E. Swelling Index

The capacity to absorb liquids, such as water, and increase in volume without dissolving is known as the swelling index. In the study of polymers, hydrogels, and other materials utilized in drug delivery systems, this property is crucial. The attributes of the pace at which active medicinal substances are released, and the overall properties of hydrophilic materials are all influenced by the swelling index. (W2 - W1) * 100/W2 is the swelling index.

Where, W1 – is the initial weight of the tablet, W2 – is the weight of hydrated tablet.

F. In-Vitro Dissolution Study

In- vitro drug release investigation of tablets was done in USP dissolving device Type 2 (paddle). The dissolving test was done using 900 mL of pH 6.8 phosphate buffer at 37 ± 0.5°C at 50 rpm. A sample (5.0 mL) of the solution was removed from the dissolving equipment at varied time intervals and the samples were replaced with new dissolution media. The samples were filtered and diluted to acceptable concentration using pH 6.8 phosphate buffer. Absorbances of these solutions were determined at 274 and 328 nm using a UV- spectrophotometer. Cumulative percentage drug release was determined using an equation developed from a standard curve.

G. Release Kinetic Study

To study the release kinetics, the data obtained from in vitro drug release studies were plotted in various kinetic models.

- **Zero order kinetics model**- Zero order, as cumulative amount of drug released versus time, describes concentration-independent drug release rate from the formulation: Qt= Q0 + kt

Where, Qt = the cumulative amount of drug released at time t
Q0 = the initial amount of drug in the dosage form.
K = is zero-order rate constant

- **First order kinetics model**- First order, as log cumulative percent drug remaining versus time, describes concentration-dependent drug release from the system. **Log C = Log C0 – kt/2.303.**

Where, C0 = the initial conc. Of drug
C = cumulative amount of drug release at time t.
K = is first-order rate constant
t = is the time in hours

- **Higuchi's square root kinetics model-** This model is based on the release of drugs from an insoluble matrix as a square root of a time-dependent process based on Fickian diffusion.

Q = KH t1/2

Where, Q = cumulative amount of drug release at time t.
KH = Higuchi constant
t = time in hours

- **Korsmeyer-Peppas equation-** This model described the drug release from a polymeric system equation. To determine the mechanism of drug release, first 60% drug release data were used in korsmeyer-peppas equation. **F = (Mt / M) = Km tn.**

Where, F = fraction of drug release at time t
Mt = amount of drug release at time t
M = total amount of drug in dosage form
Km = kinetic constant
n = diffusion or release exponent
t = time in hours

VIII. RESULT

➢ *Identification of Drug*

- *Organoleptic Properties:*

✓ *Thyme:*
- Colour: Green
- Odour: Pungent
- Taste: Slightly pungent and sweet

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✓ *Rosemary:*
- Colour: Green
- Odour: Pungent and somewhat astringent.
- Taste: Woodsy flavour with subtle notes of pepper, lemon and mint.

➢ *Solubility Study:*

Thyme is slightly soluble in water at a neutral pH, but extremely soluble in alcohols and other organic solvents. Rosemary is soluble in water, alcohol and glycerol.

➢ *Micromeritic Properties of the Granules*

Table 9: The Results of the Micromeritic Properties of the Granules are Presented

Batch No.	Angle of Repose	Bulk Density	Tapped Density	Hausner Ratio	Compressibility Index
F1	23.98	0.471	0.521	1.1	9.5%
F2	22.3	0.482	0.539	1.1	10%
F3	22.78	0.465	0.501	1.07	7.1%
F4	22.9	0.479	0.523	1.09	8.41%
F5	24.15	0.462	0.512	1.10	9.7%
F6	25.03	0.468	0.510	1.08	8.2%

The **Bulk density** of thyme and rosemary powder mixed blends prepared with hydroxypropyl methyl cellulose, was measured by graduated cylinder. The bulk density was found in the range **0.462– 0.482 kg/cm3.**

The **Tapped density** of thyme and rosemary powder mixed blends prepared with hydroxypropyl methyl cellulose, was measured by graduated cylinder. The Tapped density was found in the range **0.501– 0.539 gm/cm3**.

The **Hausner's ratio** of thyme and rosemary powder mixed blends, prepared with hydroxypropyl methyl cellulose, using bulk density and tapped density data, Hausner's ratio was calculated. It was found in the range **1.07 – 1.1**.

The **Compressibility index** of thyme and rosemary powder mixed blends, prepared with hydroxypropyl methyl cellulose, using bulk density and tapped density data, compressibility index was calculated. It was found in the range **7.1 – 10%**.

The **Angle of repose** ranged from **22.3 - 25.03**. The flow properties of powder blend in all formulations exhibit good flow characteristics

Table 10: Calibration Curve of Thyme

Thyme

Conc.	Absorbance
2ml	0.19
4ml	0.299
6ml	0.41
8ml	0.52

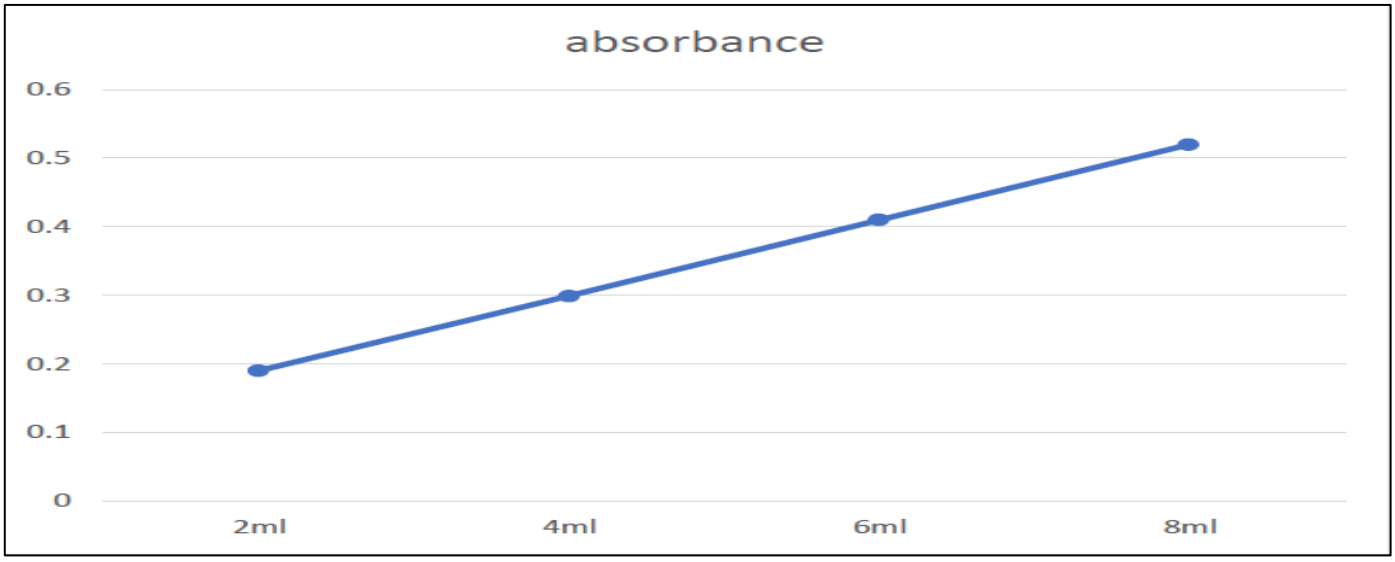

Fig 1: Absorbance of Thyme

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Table 11: Calibration Curve of Thyme and Rosemary

Conc.	Absorbance
2ml	0.129
4ml	0.287
6ml	0.455
8ml	0.62

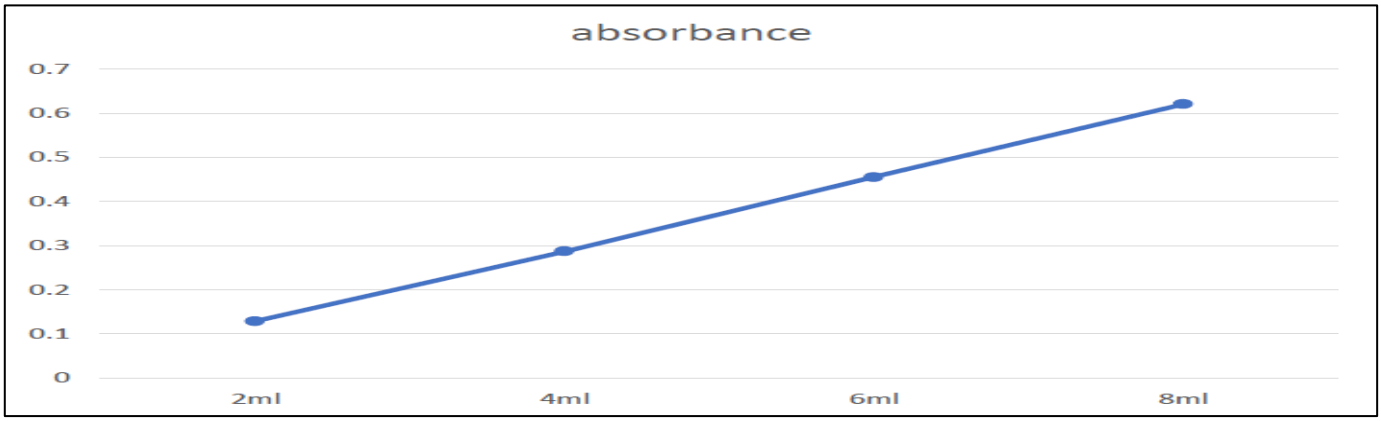

Fig 2: Absorbance of Rosemary

In-Process Quality Control Test of Controlled release tablet of thyme and rosemary

Table 12: The result of the IPQC test of the prepared tablets was done as per the procedure and presented in the table

Batch No.	Weight Variation in mg Mean ± S.D. (n=10)	Hardness (kg/cm2) (n=10)	Friability (n= 10) %	Uniformity of Content (n=5)
F1	652 ± 5	6.40	0.428	98.01
F2	647 ± 5	6.65	0.398	99.54
F3	648 ± 5	6.48	0.426	99.89
F4	650 ± 5	6.60	0.385	98.94
F5	651 ± 5	6.71	0.463	99.05
F6	650± 5	6.54	0.293	99.78

Tablets were prepared by using Direct Compression method. Since the material was free flowing, tablets were obtained of uniform weight due to uniform die fill tablets were obtained in the range with acceptable **weight variations** as per pharmacopoeia specifications, less than **5%**.

Tablets were evaluated by using **Pfizer Hardness tester**. **Hardness** of the tablets was found in the range **6.40 – 6.71 Kg/cm2**. Uniform hardness was obtained due to equal compression force.

Tablets were evaluated by using **Roche Friabilator** and **Friability** of tablets was observed in the range **0.293 – 0.463%**. **Content uniformity** of tablets was observed in the range of **98.01 – 99.78**.

Table 13: Swelling Index

Time (Hr)	F1	F2	F3	F4	F5	F6
1	2.21	4.95	3.62	6.11	7.41	6.83
2	20.63	24.53	25.92	22.43	28.72	26.89
4	45.99	46.92	48.36	46.93	51.39	49.66
8	72.21	74.4	70.60	67.49	75.47	61.42
12	83.4	82.8	80.40	86.71	92.48	72.89

Table 14: In-Vitro Drug Release Studies

Time (hr)	F1	F2	F3	F4	F5	F6
0	0%	0%	0%	0%	0%	0%
1	30.4%	28.5%	22.6%	18.7%	16.4%	11.5%
2	46.7%	43.4%	38.6%	32.1%	31.7%	26.3%
4	67.1%	60.3%	56.2%	50.3%	46.1%	40.7%
6	79.9%	78.9%	65.7%	67.8%	63.9%	54.9%

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8	86.3%	87.2%	74.5%	72.6%	71.4%	67.4%
10	90.3%	92.8%	89.4%	86.5%	85.1%	75.3%
12	96.7%	95.7%	93.7%	96.4%	97.6%	88.7%

In-vitro drug release studies were conducted for the formulation using USP dissolution apparatus type-II (paddle), at 50 rpm. The percentage drug release at the end of 24 hrs was found in the range 88 – 98 %.

Table 14: Release Kinetics Study

Batch	**Zero-Order (R2)**	**First-Order (R2)**	**Higuchi's Model** (R2)	**Krosmeyer-Peppas (K n R2)**
F1	0.9134	0.9718	0.9854	30.399 0.6193 1
F2	0.9293	0.9959	0.9884	28.499 0.6067 1
F3	0.9755	0.9978	0.9722	23.938 0.6228 0.998
F4	0.9209	0.9924	0.9887	19.359 0.6923 0.999
F5	0.9213	0.9861	0.9842	18.320 0.6772 0.995
F6	0.9432	0.9868	0.9804	14.066 0.7646 0.996

As the n value of Krosmeyer - peppas equation is more than 0.45 but less than 0.85 and r2 value an average of 0.998 which represents that it follows non-fickian transport.

IX. DISCUSSION

Millions of individuals worldwide are experiencing osteoporosis, which is characterized by increasing loss of bone mass and skeletal fragility. In the past, calcium and vitamin D3 supplements have been used as treatments to preserve bone mineral density (BMD) and stop additional deterioration of the bone structure. Nonetheless, new research has looked into alternative therapy, such as the use of herbal remedies like thyme, which may be beneficial without having the negative effects of traditional pharmaceutical treatments like HRT, bisphosphonates, and selective estrogen receptor modulators (SERMs). (Mahant et al., 2024).[5]

Ahmed R. Abu-Raghif et al. (2023) has done a comparison research to evaluate the effectiveness of thyme in treating osteoporosis in postmenopausal women vs the usual course of treatment with calcium and vitamin D3. Forty postmenopausal women with osteoporosis were split into two groups in this randomized controlled trial: one group received 500 mg of thyme capsules twice a day, while the other received 600 mg of calcium and 500 IU of vitamin D3 supplements once a day. The study monitored changes in BMD, T-score, serum ionized calcium, and erythrocyte sedimentation rate (ESR) at regular intervals throughout a six-month period.[7]

The results of this study highlighted the potential of thyme as an effective natural alternative for osteoporosis treatment. The group treated with thyme demonstrated a significant increase in BMD and T-score after six months compared to both the baseline measurements and the group treated with calcium and Vitamin D3 (Abu-Raghif et al., 2023). Additionally, there was a marked reduction in mean serum ionized calcium and ESR in both groups, although the improvements were more pronounced in the thyme-treated group. These findings align with other research emphasizing the osteoprotective properties of thyme, particularly its ability to stimulate osteoblast activity and inhibit osteoclast function, as noted by Marta Trzaskowska et al. (2020).[3]

In conjunction with the findings from the thyme and rosemary formulations discussed earlier, this comparative study reinforces the idea that herbal remedies can serve as viable alternatives to traditional treatments. The compressibility and release profiles of thyme-based formulations, as demonstrated in previous studies (Elbahnasawy et al., 2020), support their potential for widespread use. The ability of thyme to enhance BMD and modulate inflammatory markers like ESR makes it an attractive option for long-term management of osteoporosis, especially in postmenopausal women, where bone loss is more pronounced due to hormonal changes.[1]

Moreover, Abu-Raghif et al.'s findings align with the notion that thyme's antioxidant and anti-inflammatory properties may contribute to its ability to reduce bone resorption and enhance bone formation. This complements the research of Mahant et al. (2024), which suggests that natural compounds such as thyme and rosemary could provide safer, affordable, and effective treatment alternatives, reducing reliance on therapies that carry higher risks of side effects.

As the search for safer and more natural alternatives to osteoporosis treatment continues, the integration of thyme and rosemary into controlled-release formulations offers significant promise. In conclusion, the findings from both Mahant et al. (2024) and Abu-Raghif et al. (2023) highlight the growing importance of herbal remedies in managing bone health and preventing fractures in osteoporotic patients, particularly postmenopausal women.[5,7]

X. CONCLUSION

Fragile and weak bones are symptoms of osteoporosis. It often happens when the rate of new bone formation is lower than the rate of old bone loss. Rosemary and thyme both promote healthy bone growth by preventing its resorption. They are also useful in preventing bone loss caused by a lack of calcium. A potential new treatment strategy for

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osteoporosis is the creation of a controlled-release pill that uses the active pharmaceutical ingredients (API) of thyme and rosemary. Thyme and rosemary include bioactive chemicals that have anti-inflammatory and antioxidant effects, which improve bone health by decreasing bone resorption and increasing bone density, according to this study. To maximize the drug's therapeutic action at the plasma level and limit the risk of side effects, a controlled-release tablet is used. This assures that the compounds will be released in a regulated manner. By demonstrating that the controlled release system effectively maintains the therapeutic level of medicine in the body, the in-vitro evaluation enhances both patient compliance and the efficacy of therapy. The current investigation set out to design and assess a direct compression technique controlled release tablet containing rosemary and thyme. The controlled release tablet is made using thyme and rosemary as an active pharmaceutical ingredient (API). Seventy milligrams of thyme and four hundred milligrams of rosemary are utilized. The controlled release of the tablet in this study is achieved by using HPMC as a polymer in conjunction with the wet granulation process. HPMC is added to each batch at varying concentrations to find the optimal batch for the controlled release of the tablet. Lactose serves dual purposes in the formulation: as a sweetener and a filler. For controlled-release formulations, it is the filler and sweetener that is employed most frequently. One percent weight by weight of the pill is talc, which is utilized as a diluent in the formulation. One percent weight by weight of the pill is magnesium stearate, which is utilized as a lubricant in the formulation. Formulas 1–5%, 2–7.5%, 3–10%, 4–12.5%, 5–15%, and 6–17.5–% HPMC are extracted from the total tablet weight. Granules generated using the wet granulation method were found to be adequate for further investigations based on the acceptable results shown by the formulation's angle of repose, bulk density, tapped density, car's index, and Hausner's ratio value. All of the in-process quality control tests, including those for consistent content, hardness, friability, and weight fluctuation, were determined to be within the permitted range according to IP. F1: 96.7%, F2: 95.7%, F3: 93.7%, F4: 96.4%, F5: 97.6%, and F6: 88.7% of the medication has been released after 12 hours. In which F5 is determined to be a batch that is optimized. Researchers have shown that when the polymer concentration increases, the medication releases more slowly in vitro. As time goes on, the rate of medication release slows down. After 12 hours, the swelling index of the F5 batch is 92.48%. F5 batch follows the non-fickian transport, as shown by the n value of 0.67 in the Krosemeyer-Peppas equation. So, the medicine is released by diffusion and swelling, and the rate of release depends on the passage of time. The aforementioned research concludes that thyme and rosemary controlled release formulations utilizing HPMC as a rate-controlling polymer and the direct compression approach will give the medication a steady release throughout time.

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