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Formulation Design and In Vitro Evaluation of Dutasteride Orodispersible Tablets Using super disintegrants

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ABSTRACT
Benign prostatic hyperplasia(BPH), also known as enlarged prostate symptoms in males, is treated with dutasteride. The liver substantially metabolizes dutasteride. Because it skips metabolism, the orodispersible tablet was a good dose to overcome these problems. The BCS categorization for dutasteride is class II. The current research attempted to design and develop an orodispersible tablet containing dutasteride using croscarmellose sodium, povidone, and sodium starch glycolate as superdisintegrants. This was done to achieve rapid disintegration when held beneath the tongue, which would allow for direct absorption of the active ingredient by the oral mucosa, thereby avoiding fast-pass metabolism and increasing the bioavailability. Wet granulation techniques were used to create dutasteride orodispersible granules, and the evaluation of all precompression parameters fulfilled the acceptance standards, demonstrating the granules' outstanding flow characteristics. Different post-compression characterizations of the tablet were conducted, and the results complied with pharmacopeia requirements. In vitro, release studies were carried out with dissolution equipment of the USP II paddle type for a variety of different formulations. Investigations into the in vitro release kinetics of both the zero-order and the first-order kinetic models were carried out. FTIR tests revealed that the drug and the excipients were not incompatible with one another. Following the foregoing formulations, the drug and polymers are thermally stable, according to DSC investigations that were conducted to determine the thermal stabilities of the drug and the physical mixture of the drug and excipients employed in formulation. To verify the stability of dosage forms, accelerated stability studies were conducted, and the optimized formulation was discovered to be stable to an acceptable range.

Key Words: Orodispersible, Dutasteride, Croscarmellose Sodium, crospovidone, Sodium starch glycolate

I. INTRODUCTION

While there are a number of ways to give medications and other systemic treatments, the oral route is considered to be the most effective and has the best patient compliance [1]. Orally disintegrating tablets have markedly increased rates of drug absorption, disintegration, clinical impact onset, and bioavailability in comparison to traditional dose forms [2-4]. Making the tablet more porous by the use of appropriate disintegrating agents and high water-soluble excipients in the formulation is the basic process for producing ODTs [5]. These dosage forms dissolve in the mouth and release the drug as soon as they come into contact with saliva. The fact that water is not needed while administering medication makes it even better for elderly and paediatric patients [6].

Tablets without coatings that dissolve fast in the mouth before swallowing are known as orodispersibles. Orodispersible pills are sometimes referred to as "melt-in-the-mouth tablets," "mouth-dissolving tablets," "Rapimelt tablets," "Porous tablets," and "Quick-dissolving tablets". The term ODT was recently approved by the British Pharmacopoeia, the US Pharmacopoeia, and the CDER (Centre for Drug Evaluation and Research). The US Food and Drug Administration describes ODT as a solid dosage form made up of pharmaceutical components that dissolve rapidly on the tongue [7, 8].

The European Pharmacopoeia defines ODT as "A tablet which is to be placed in the mouth and disperses rapidly within three minutes before swallowing".Elderly folks find it challenging to deliver traditional pills since they require them daily to maintain their healthy lifestyles. Due to their immature neurological and muscular systems, children may also have trouble swallowing pills; patients who travel may also have this problem. Orodispersible patents, which enable scientists to create and develop a medicine into a

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novel dosage form, can be used to address these problems[9].

In addition to treating BPH symptoms, Dutasteride may lower the risk of acute urine retention, or the sudden inability to pee. Additionally, dutasteride may lessen the need for prostate surgery. Dutasteride blocks the conversion of testosterone to DHT, which has a stronger affinity for androgen receptors, by forming a stable complex with 5α-reductase. DHT controls the genes that control cell division by acting on certain receptors. After taking one soft gelatin capsule containing 0.5 mg, the time to peak blood concentrations (Tmax) of dutasteride happens in two to three hours. In five healthy persons, the range of absolute bioavailability is around 40% to 94%. Dutasteride is well attached to plasma proteins (>99.5%) and has a broad volume of distribution (300 to 500 L). In serum, 96.6% of Dutasteride is attached to α-1 acid glycoprotein and about 99% is associated with albumin. CYP3A4 and CYP3A5 mediate the substantial hepatic metabolism of Dutasteride. The primary method of removing dutasteride is metabolism. Dutasteride is mostly excreted as metabolites in the faeces (40%). The linear clearance of dutasteride was just 0.58 L/h. At a steady state, the half-life of dutasteride terminal elimination is around 5 weeks. Due to its limited water solubility, dutasteride is only commercially accessible on the market as a soft gelatin capsule format and is classed as Biopharmaceutics Classification System (BCS) class II. Dutasteride melts between 242° and 250°C, and it is a white to pale yellow powder. It is insoluble in water but soluble in ethanol (44 mg/mL), methanol (64 mg/mL), and polyethylene glycol 400 (3 mg/mL). [10]

To achieve rapid dispersion when taken through the buccal cavity and rapid onset of action, the main goal of the current studies was to create and conduct in vitro evaluation tests of orodispersible Dutasteride tablets using super disintegrants like sodium starch glycolate, croscarmellose, and crospovidone.

II. MATERIALS AND METHODS

Materials

Dutasteride was received as a gift sample from Dr. Reddy's LaboratoriesPvt. Ltd. in Hyderabad, India. Also provided byDr. Reddy's Laboratories Pvt. Ltd. was a gift sample of the superdisintegrant sodium starch glycolate, croscarmellose, and crospovidone. The diluent was purchased from Otto Manufacturers. Lactose, PVP K30, talc, and magnesium stearate were purchased from S.D. Fine Chemicals Pvt. Ltd. in Mumbai, India. Each component was of the highest calibre for a lab. The double distillation method was used in the lab to produce the distilled water that was used in the study.

METHODS

Analytical method for the in vitro estimation of Dutasteride in the formulations

Using a 6.8 pH phosphate buffer, a main stock solution of dutasteride at a concentration of 1000 g/ml was prepared. Using the same phosphate buffer pH 6.8, a secondary stock solution was prepared from the original stock solution at a concentration of 10 g/ml after the appropriate dilution. The maximum absorbance of the produced secondary stock solution was discovered to be 242 nm; this value was chosen and utilized for more research. After scanning the fluid at wavelengths spanning from 400 nm to 200 nm using an Analytical Technologies Ltd. Spectro 2080 UV spectrophotometer, this was discovered. The secondary stock solution was first diluted to yield a range of concentrations of 2, 4, 6, 8, and 10 µg/ml using the same phosphate buffer pH 6.8. The matching absorbance was then calculated at the maximum wavelength of 242 nm. The pure Dutasteride calibration curve was made by plotting the measured absorbencies against corresponding concentrations. [11]

Drug and excipient compatibility studies

The medication and excipients used to make different batches of Dutasteride orodispersible tablets were analyzed for possible physical and chemical interactions using FTIR and DSC.

Fourier Transform Infrared (FTIR) spectroscopy

Fourier transform infrared (FTIR) spectroscopy was conducted to identify the peaks in both the pure drug and the excipients, which signify the presence of specific functional groups. The compatibility of the drug and excipients is established if the functional groups in the pure drug are mirrored in the formulations. FTIR analysis was performed on both the pure drug and a physical mixture of the drug with all excipients (optimized formulation) for Dutasteride. Potassium bromide (KBr) pellets were employed in this technique. The components were triturated with KBr, and a pellet was formed by applying a pressure of 100 kg/cm²

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for two minutes. The resulting pellet was analyzed using the FTIR 8400S by Shimadzu, Japan. The analysis commenced with the test samples, followed by the acquisition of the KBr background. Identical procedures were executed for the analysis of the drug, each excipient, and the physical mixture of the excipients and the drug. [12]

Differential scanning calorimetry (DSC) research

Thermal analysis using DSC or TGA techniques may also be used to analyze the physical interaction between a medicine and the polymers employed in the formulation of various dosage forms. In the current investigations, a Shimadzu DSC 60 from Japan was utilized to perform a DSC analysis of dutasteride and the physical combination of drug and excipients (optimized formulation) employed in the formulation of dutasteride orodispersible tablets to assess the probability of polymer-drug thermal interaction. This was done to determine whether or not the polymer and drug had a thermal interaction. After carefully weighing the samples, which ranged in weight from 5.6 mg to 5.6 mg, they were hermetically sealed in an aluminium crucible and heated continuously at a rate of 10 degrees Celsius per minute between 40 and 300 degrees Celsius. To maintain an inert environment, 50 ml/min of nitrogen gas flushing was applied to the region.

Formulation of DutasterideOrodispersible tablets (DRF_1-DRF_{10})

Dutasteride orodispersible tablets were made using the wet granulation technique. Before being employed in the finished goods, each component was meticulously measured and filtered through a No. 80 mesh screen. After being evenly combined and sieved through #20, powders including aspartame, lactose, croscarmellose sodium, crospovidone, sodium starch glycolate, and dutasteride were added. The starch (insoluble) paste was then utilized as a binder. To lower the moisture content and stop the aggregates from sticking to the filter, they were dried for five to ten minutes after the binder was added. Granules were created by processing the aggregates using filter #20. The granules are dried for 20 minutes at 40 degrees Celsius, resulting in a 2- to 5% reduction in moisture content. For two to three minutes, dry granules were combined with talc and magnesium stearate as lubricants. The formulations' bulk densities, tapped densities, compressibility indices, and Hausner's ratios were measured before compression. We compacted the sample grains into tablets for testing using a 10-station rotary punching machine (Saimach Pharmaceutical Pvt. Ltd.) and 6mm concave punches. Dutasteride comes in 100 mg tablets with dosages of 0.5 mg. Table 1 is a list of the several formulas that were created using the same technique. The drug content, hardness, friability, and in vitro dissolving of the orodispersible tablet formulations were examined after compression, among other post-compression parameters. [13]

Table 1: Compositions of different formulations of DutasterideOrodispersibletablets

F. No.	DRF_1	DRF_2	DRF_3	DRF_4	DRF_5	DRF_6	DRF_7	DRF_8	DRF_9	DRF_{10}
Dutasteride (mg)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Croscarmellose Sodium (mg)	3	4	---	---	---	---	2	---	2	2
Crospovidone (mg)	---	---	3	4	---	---	2	2	---	1
Sodium starch Glycolate (mg)	---	---	---	---	3	4	---	2	2	1
Lactose (mg)	83	81	83	81	83	81	81	81	81	81
Starch (Insoluble) (mg)	10	10	10	10	10	10	10	10	10	10

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Mg. Stearate (mg)	2	2	2	2	2	2	2	2	2	2
Talc (mg)	1	1	1	1	1	1	1	1	1	1
Aspartame (Mg)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Total Wt. (mg)	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**

Evaluation of precompression parameters of dry granules of DutasterideOrodispersibletablet formulations

AngleofRepose(θ)

A funnel attached to a stand at a specific height (h) was used to let the dry granules pass through. Then, by determining the height and radius of the granule heap that had formed, the angle of repose was determined.

$$\theta = \tan^{-1}\left(\frac{h}{r}\right)$$

where the granule heap's height and radius were represented by h and r, respectively, and θ was referred to as the angle of repose. The requirements state that an angle of repose value of less than 25^0 denotes excellent flow while an angle of more than 40^0 denotes bad flow. [14]

Bulk density and tapped density

The following formulae were used to calculate the produced Dutasteride Orodispersible dry granules' bulk density (BD) and tapped density (TD) for each formulation. [15]

$$BD = \frac{\text{weight of the dry powder}}{\text{volume of the packing}}$$

$$TD = \frac{\text{weight of the dry powder}}{\text{tapped volume of the packing}}$$

CompressibilityIndex (Carr's index):

By comparing the bulk density (BD), tapped density (TD), and rate of granule packing down, one may assess the flow capabilities of both powder and granule. The produced Dutasteride Orodispersible dry granules' compressibility index, or Carr's index, was determined using the following formula.

$$\text{Carr's index (\%)} = \frac{TD - BD}{TD} \times 100$$

As to the standard, exceptional flow is indicated by Carr's index values "between" 5 and 15, while good flow is indicated by values between 12 and 16. Values "between" 18 and 21 denote adequate, whereas values "between" 23 and 25 denote subpar. "Between" 33 and 38 denotes extreme poverty, while more than 40 denotes extreme poverty. [16]

Hausner'sratio:

The following formula was used to find Hausner's ratios of the produced Orodispersible dry granules of dutasteride.

$$\text{Hausner's ratio} = \frac{TD}{BD}$$

Values below 1.25 (i.e., 20% of Carr's index) indicate excellent flow, whereas values over 1.25 (i.e., 33% of Carr's index) indicate bad flow. To increase flow, a glidant must be applied between 1.25 and 1.5. [17]

Evaluation of post-compression parameters of DutasterideOrodispersible tablets formulations

Each formulatedorodispersible tablet formulation was assessed according to the following criteria.

Shape of Tablets

The Indian Pharmacopoeia defines pharmaceutical tablets as solid, flat, or biconvex discs, serving as a unit dose form, produced by compressing a medication or a combination of pharmaceuticals, with or without diluents. Research indicates that oval pills may facilitate simpler ingestion and offer a more rapid esophageal transit time compared to round tablets. The dimensions and form of the pill may also affect patient adherence to pharmaceutical protocols. The tablets' configurations were ascertained after meticulous examination using a magnifying glass.[18]

Average thickness

We randomly selected 10 tablets from each formulation of Dutasteride orodispersible tablets to compare their thickness. The thickness of each tablet was quantified with a digital Vernier caliper (a Mitutoyo dial thickness gauge, manufactured in Japan), with findings presented as the mean of 10 measurements together with the standard deviation. The thickness of a tablet can be

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measured using a micrometer or other instruments. The thickness of the tablet must be regulated within a ± 5% deviation from the standard value. Distinctive identifying marks: These markings employ methods such as embossing, engraving, or printing. [18]

Tablet Hardness

"Tablet hardness" quantifies the force necessary to fracture a tablet using a testing instrument that subjects the tablet to tensile or bending stress. The hardness of all Dutasteride Orodispersible tablet formulations was evaluated using a Monsanto hardness tester (Cad Mach). The tablet is positioned between the anvils or platens of the testing apparatus. A force is incrementally exerted on the tablet until it breaks. The force at which the tablet fractures is documented as the tablet's hardness. Ten orodispersible tablets with known weights from each formulation were evaluated for crushing strength, measured in kg/cm², averaged, and presented with standard deviation. The hardness test of the material reflects its strength. The primary physical characteristic for evaluating tablets is hardness. The permissible hardness range for a tablet is 5–8 kg. A force ranging from 4 to 10 kg is deemed acceptable. [19]

Friability

Ten pills from each previously weighed batch were put in the Roche friabilator (Roche friabilator, Secor India, Delhi, India). Tablets were discovered following one hundred spins of the friabilator. The pills were subsequently dusted, and the remaining total weight was recorded. This formula was employed to assess friability.

$$\%F = \frac{(Wi - Wf)}{Wi} \times 100$$

W_i and W_f represent the initial and final weights of the tablets prior to and subsequent to the friability test. Tablets that exhibit a weight loss of less than 0.1% to 0.5%, with a maximum permissible loss of up to 1% of their weight, are deemed acceptable. [20]

Weight variation test

The weight variation statistical quality control test is employed to verify the consistency of the dosage unit, hence ensuring product safety, identification, and quality. Weight variation for all Dutasteride orodispersible tablet formulations was evaluated according to USP standards. Twenty tablets from each batch were weighed collectively and individually using an automated balance. Calculations were conducted on the mean weight and percentage variation of each pill. The accompanying formulae are employed for the computation of weight variation:

Weight Variation = $(I_w - A_w) / A_w \times 100\%$,

where I_w represents the individual weight of the tablet and A_w denotes the average weight of the tablet. The USP standard specifies that the weight variation tolerance limit for uncoated tablets is 10% for those averaging 130 mg or less, 7.5% for tablets averaging between 130 and 324 mg, and 5% for tablets averaging more than 324 mg. The tablet's weight shall not vary from the average weight by more than the weight of two tablets, and no individual tablet may depart by more than 15%. [21]

Content uniformity

Content uniformity is a critical quality metric for the final solid dosage form, ensuring that a constant amount of the active pharmaceutical ingredient is preserved throughout batches, hence guaranteeing the patient receives the appropriate dosage. Twenty pills were pulverized to evaluate the uniformity of the content across all formulations. One tablet of powder was dissolved in 100 cc of phosphate buffer at a pH of 6.8 and heated at 37 °C for 15 to 20 minutes with constant stirring. The Dutasteride concentration was quantified utilizing a UV Spectrophotometer (Analytical Technologies Ltd. Spectro 2080) at 242 nm following the cooling, filtration, and proper dilution of the fluid. The mean drug content of each formulation was calculated following each measurement conducted in triplicate. [22]

Wetting time and water absorption ratio

The disintegration of the tablet formulation is indicated by the wetting time. The disintegration rate rises as wetting time diminishes. A double-layered tissue paper was positioned in a petri dish with an internal diameter of 6.5 cm, containing 10 ml of phosphate buffer at pH 6.8 and 0.1% w/v methylene blue to assess the wetting time. The tissue paper surface in the petri dish was meticulously coated with one tablet from each variant of Dutasteride orodispersible tablet. The wetting time was quantified as the duration required for the dye to ascend to the tablet's upper surface. Standard deviations were computed, and measurements were conducted in triplicate. By measuring the tablet's weight (Wb) before to its placement on the Petri dish and subsequently after the wetting time, one may ascertain the water absorption ratio (R). The damp pill was removed

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and reweighed (Wa). The below equation was employed to determine the water absorption ratio. [23]

$$R = \frac{(Wa - Wb)}{Wb} \times 100$$

Invitro disintegration time (D_t)

The disintegration of a tablet is essential since it facilitates the dissolving of the pharmacological component. The USP designates 2 minutes as the permissible time frame for tablet disintegration that complies with official standards, while also stipulating 2 minutes for orodispersible dosage forms when employing the disintegration device for oral tablets devoid of the plastic covering discs. The test utilized tablet disintegration equipment (model EI D-16, Electrolab, Mumbai, India). An altered disintegration technique was employed to perform an in vitro disintegration test using a disintegration tester maintained at 37°C ± 0.5°C in phosphate buffer at pH 6.8 (n = 6). The duration required for each pill to completely decompose into smaller particles was monitored while the pills were contained in the basket. [24]

Invitro drug release (dissolution) study

Dissolution testing is a vital invitro technique in the pharmaceutical industry that yields significant data on the dissolving characteristics of solid oral dosage forms. It enables scientists to quantify the rate of drug release from its dosage form into the surrounding aqueous medium inside the specified device. The in vitro dissolution study for all formulations was conducted using an eight-station USP dissolution rate test equipment type-II (LABINDIA DS 8000, Mumbai, India). The dissolving media, including 900 cc of phosphate buffer at pH 6.8, was maintained at 37°C ± 0.5°C while agitating at 50 rpm. At regular intervals, 5 ml aliquots were extracted and substituted with an equal volume of fresh dissolving media. Samples were collected at five-minute intervals and subsequently filtered with Whatman filter paper. Dutasteride released from orodispersible tablets was detected in samples using spectrophotometric analysis at 242 nm. Significant variability in outcomes might hinder the identification of trends or the impact of formulation modifications. Dissolution findings are deemed extremely variable if the relative standard deviation (RSD) exceeds 20% at time intervals of 10 minutes or less, and surpasses 10% RSD at subsequent periods. [25]

Characterization of the in vitro drug release profile

The release rate and mechanism of Dutasteride from formulated orodispersible tablets were evaluated by applying the dissolving data to specific exponential equations.

The zero-order release equation is determined using the following formula.

$$Q = K_0 t$$

Q represents the quantity of medication released at time t, whereas K_0 denotes the zero-order release rate constant.

The first-order equation is determined by using the specified formula.

$$\log(100 - Q) = \log 100 - K_1 t$$

K_1 denotes the first-order release rate constant.[26]

Stability studies of the best formulation

The objective of stability testing is to furnish evidence regarding the variation in the quality of a drug substance or product over time, influenced by various environmental factors such as temperature, humidity, and light, and to determine a re-test period for the drug substance or a shelf-life for the drug. Research on the short-term stability of Dutasteride orodispersible tablets' optimum formulation was undertaken by ICH guidelines. The optimal formulation was subjected to accelerated stress conditions for 90 days at 40 °C ± 2 °C and 75% ± 5% relative humidity. Subsequently, the product's friability, hardness, weight fluctuation, thickness, drug content, and in vitro drug release studies were evaluated. [27]

III. RESULTS AND DISCUSSION

Drug-Excipient Compatibility studies by FTIR:

The FTIR spectra of Dutasteride in its pure form and a physical mixture with the excipients used in its manufacturing are shown in Figures. The broad peak that appeared at 3585 cm^{-1} also appears in Dutasteride with excipients used in formulation at 3587 cm^{-1}due to N-H stretching, and the sharp peaks that appear in spectra of Dutasteride at 2853 cm^{-1}also appear in physical mixtures of Dutasteride with excipients used in formulation, according to a comparison of the IR spectra of Dutasteride and Dutasteride with excipients used in formulation When Dutasteride is physically mixed with formulation excipients, the broad peak that was visible at 3095 cm^{-1}appears at 3120 cm^{-1} due to CH stretching (Alkene). The typical IR absorption peaks of dutasteride at 1700 cm^{-1}(C=O stretching (Amide)), 1545 cm^{-1} (N-H bending), 1340 cm^{-1}(CH bending (alkane)), 1415

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cm^{-1}(C-N vibration), and 880 cm^{-1}(CH bending (aromatic)) were also present in the physical mixture of dutasteride with excipients used in formulation, with no shift in the major peaks and no additional. The FTIR spectra of the pure drug Dutasteride and the best formulations are shown in **Figures1 and 2**.

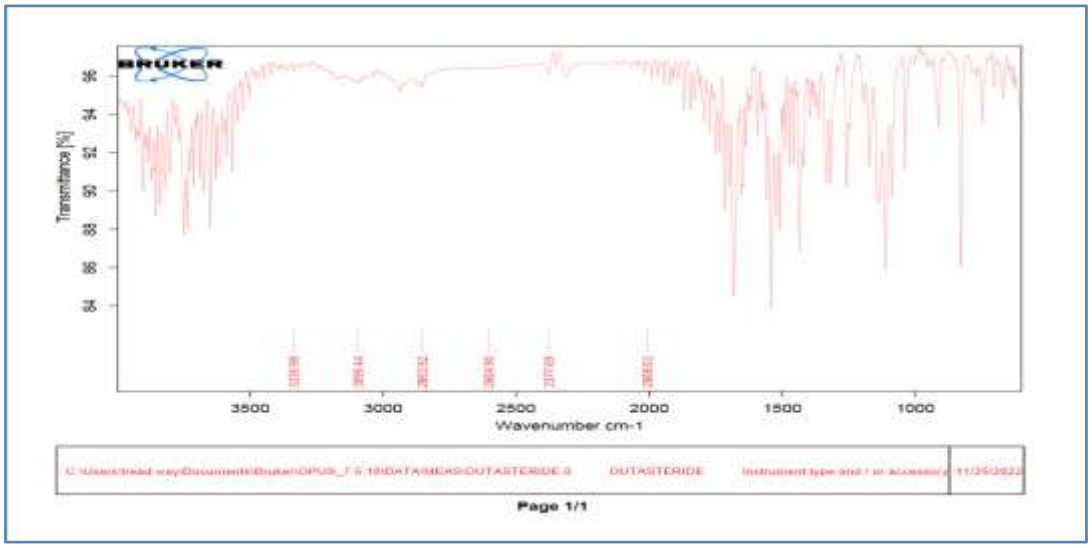

Fig. 1: FT-IR spectra of Dutasteridepure drug

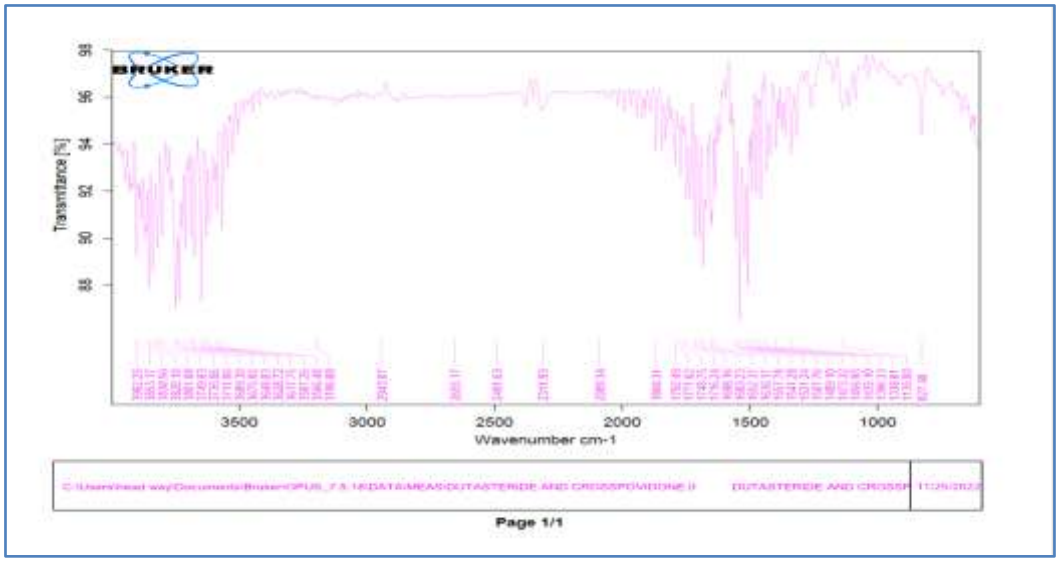

Fig. 2: FT-IR spectra of physical mixture of Dutasteride with excipients

Drug-Excipient thermal Compatibility studies by DSC Research

To rule out any potential drug and polymer thermal interaction, a DSC thermogram of dutasteride and a physical combination of dutasteride with excipients were obtained. The endothermic peaks that appeared in the physical mixture of the drug and excipients utilized to produce the orodispersible tablet formulation and the pure drug were compared in this investigation. It was noted that the endothermic peak for dutasteride appeared at 244.45^{o}C and 244.8^{o}C in the physical mixture. The physical mixture's DSC thermogram showed an endothermic peak at 150.5 ^{o}C and 204.2 ^{o}C, respectively, due to the excipients crospovidone, croscarmellose sodium, and sodium starch glycolate. According to the aforementioned DSC investigations, the formulation is thermodynamically stable because it required approximately the same amount of heat as the pure

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medication and the inclusion of various excipients in the drug didn't result in any thermal changes. Additionally, no endothermic to exothermic peak shifting was observed. The DSC thermograms for Dutasteride and the physical mixture of Dutasteride and excipients used in the production of orodispersible tablets are shown in Figures3 and 4, respectively.

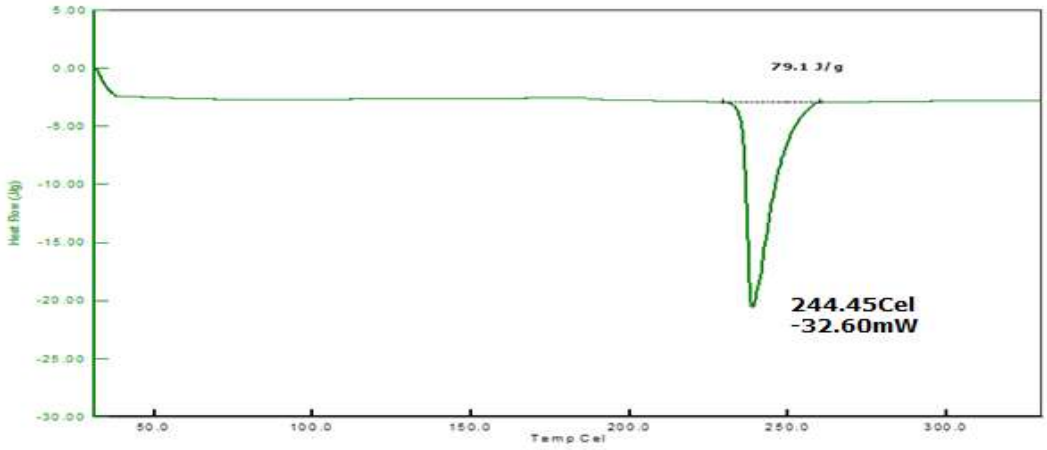

Fig. 3: DSC Thermogram of Dutasteride pure drug

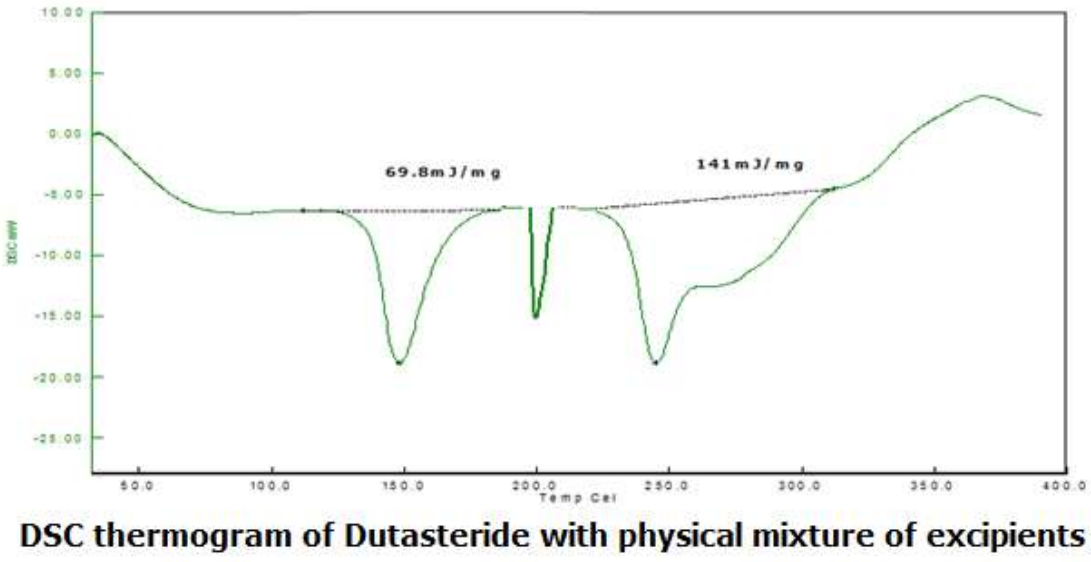

Fig. 4: DSC Thermogram of physical mixture of Dutasteride with excipients

Pre-Compression parameters

Wet granulation is a common and more advantageous process for creating tablet granules than other ones. An accumulation of separate particles linked together by bonds with a finite strength is referred to as a granule. In a heterogeneous formulation, the physical characteristics of the granules, such as their surface area, shape, hardness, and size, can have a considerable impact on the rate of drug dissolution and, consequently, their total bioavailability. The values for the angle of repose were discovered to be between 19.47±0.14 to 23.66±0.14. The results for tapped bulk density (TBD) and loose bulk density (LBD) vary from 0.306±0.04 to 0.356±0.02and 0.363±0.06 to 0.385±0.02, respectively. Carr's index and Hausner's ratio are calculated using these numbers. The values of the

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Carr's index were discovered to be between 9.09 % to 15.34%. This shows that granules have excellent flow characteristics. The granules had the necessary flow quality for compression, as shown by Hausner's ratio values, which were determined to be in the range of 1.07-1.18. In Table2, all pre-compression parameter values that were obtained for all formulations are listed.

Table 2: Evaluation of pre-compression parameters of formulated DutasterideOrodispersible granules

F. No.	Bulk density (gm/ml)	Tapped density (gm/ml)	Angle of repose (θ)	Carr's Index (%)	Hausner's ratio
DRF_1	0.325±0.04	0.382±0.03	22.27±0.20	14.92	1.18
DRF_2	0.356±0.02	0.408±0.05	20.45±0.12	12.74	1.07
DRF_3	0.334±0.03	0.381±0.04	23.66±0.14	12.34	1.17
DRF_4	0.306±0.04	0.354±0.02	21.35±0.13	13.56	1.16
DRF_5	0.312±0.05	0.363±0.06	22.40±0.14	14.04	1.16
DRF_6	0.315±0.06	0.366±0.04	21.72±0.15	13.93	1.16
DRF_7	0.340±0.06	0.374±0.05	23.51±0.12	9.09	1.10
DRF_8	0.336±0.04	0.385±0.02	20.60±0.17	12.72	1.15
DRF_9	0.320±0.04	0.378±0.05	21.36±0.15	15.34	1.18
DRF_{10}	0.337±0.05	0.379±0.03	19.47±0.14	11.08	1.12

All values are expressed as average± SD; (n=3)

Post-Compression parameters

Tablets from each batch of formulation were examined under a microscope and revealed to be round and without cracks. Each batch had a consistent thickness. All of the tablet weights were uniformly below 5% and had modest standard deviation values. The range of measured hardness is between 3 and 4 Kg/cm^2. Tablet hardness increased as compression force and super-disintegrant usage were both reduced. This guarantees all batches will have good handling characteristics. All of the formulations' percent friability is less than 1%, ensuring that the tablets were mechanically stable. The formulations' disintegration times, which range from 1 to 2 minutes, are within acceptable bounds for orodispersible tablets. All of the formulations' wetting times were determined to be between 52±0.21 sec to 99±0.62 sec. The formulation F_{12} had the lowest wetting values, while the formulations DRF_1 and DRF_3 had the highest wetting values. In Table3, the post-compression values for all formulations were displayed.

Table3:Evaluation of Post-compression parameters of Dutasteride Orodispersible tablets

F. code	Hardness (kg/cm^2)	Weight Variation (%)	Friability (% w/w)	Thickness (mm)	Drug content uniformity (%)	D_t (Sec)	Wetting time (Sec)	Water absorption ratio
DRF_1	3.77±0.5	4.12±0.26	0.59±0.04	3.45±0.33	98.25±1.2	142±0.28	99±0.62	15.67±0.26
DRF_2	3.25±0.4	4.21±0.18	0.64±0.04	3.56±0.22	99.51±1.1	106±0.36	83±0.54	17.54±0.30
DRF_3	3.64±0.5	4.15±0.46	0.52±0.05	3.40±0.15	99.56±1.4	114±0.47	99±0.60	14.57±0.30
DRF_4	3.15±0.5	4.24±0.34	0.68±0.03	3.44±0.11	98.54±1.2	98±0.25	72±0.25	21.62±0.52
DRF_5	3.89±0.6	3.96±0.52	0.58±0.05	3.38±0.16	102.52±1.2	124±0.37	84±0.36	12.50±0.42
DRF_6	3.31±0.5	3.94±0.85	0.65±0.05	3.45±0.15	100.61±1.4	104±0.45	68±0.32	20.37±0.32
DRF_7	3.28±0.6	4.21±0.58	0.64±0.04	3.55±0.16	101.67±1.3	95±0.39	64±0.37	22.62±0.51
DRF_8	3.31±0.5	3.95±0.32	0.65±0.05	3.28±0.18	99.20±1.2	82±0.42	55±0.36	26.40±0.35
DRF_9	3.29±0.5	3.94±0.46	0.68±0.05	3.45±0.13	98.35±1.4	96±0.38	54±0.45	22.62±0.42
DRF_{10}	3.29±0.6	4.25±0.56	0.67±0.04	3.42±0.18	99.41±1.3	78±0.42	52±0.21	27.72±0.32

All values are expressed as average± SD; (n=3)

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In vitro drug release properties

Using a USP type-II paddle-type dissolution device, the in vitro drug release properties of Dutasteride orodispersible tablets were investigated for 45 minutes in phosphate buffer pH 6.8 dissolution media. By boosting the superdisintegrant concentration to an ideal concentration of 4%, the rate of dissolution increased. While formulation DRF_1 with 3% Crosscarmellose Sodium released 99.52% of the medication in 40 minutes, concentrations of Crosscarmellose Sodium up to 4% (DRF_2) resulted in a 99.45% cumulative drug release in 35 minutes. In comparison to formulation DRF_3, which had 3% of Cross povidone, DRF_4 released 99.30% of the medication in 40 minutes while formulation DRF_3 contained 4% of Cross povidone. When compared to formulation DRF_6, which had 4% of sodium starch glycolate, formulation DRF_5 released 99.75% of the medication in 40 minutes while formulation DRF_6 had 3% of sodium starch glycolate.When two superdisintegrants are used together at a total concentration of 4%, the dissolving profile is improved and the medicine is released virtually completely within 30 minutes. Formulation DRF_{10}, which has the best initial release rate among all formulations and contains all three superdisintegrants in a concentration of 4% (2% Crosscarmellose, 1% Cross povidone, and 1% Sodium starch Glycolate), releases the medication more than 99% within 30 minutes. Figure 5 display the dissolving profiles of all formulations (DRF_1 to DRF_{10}).

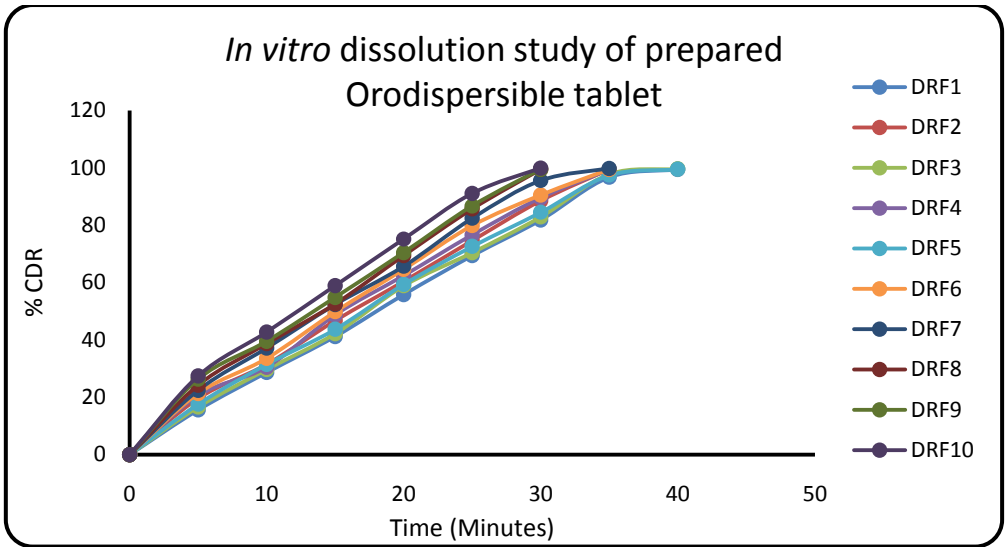

Fig. 5: In vitro drug release study of DutasterideOrodispersible tablet formulations (DRF1-DRF10)

In vitro drug release kinetics studies:

Based on having the highest dissolving profile, the formulation DRF_{10} was chosen for drug release kinetics and mechanism of drug release studies. The graphs in **Figures6 and 7** were created by fitting the in vitro dissolving data of Dutasteride orodispersible tablets (DRF_{10}) in various kinetic models, including zero-order and first-order equations. The drug release mechanism for the Dutasteride orodispersible tablet in the current investigation was determined to be anomalous diffusion coupled with erosion since the zero-order kinetic curve demonstrated the highest regression value. Regression values of an improved Dutasteride orodispersible tablet (DRF_{10})from an in vitro release kinetic investigation are shown in Table 4.

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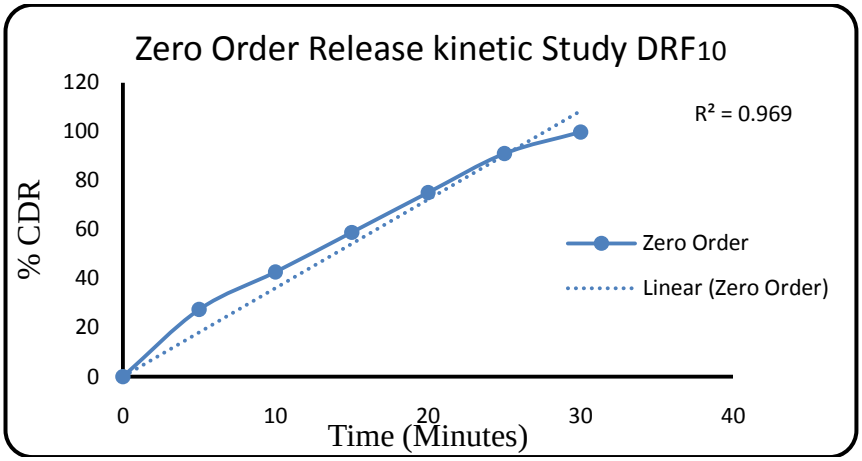

Fig. 6: Zero order release kinetic study of best formulation DRF10

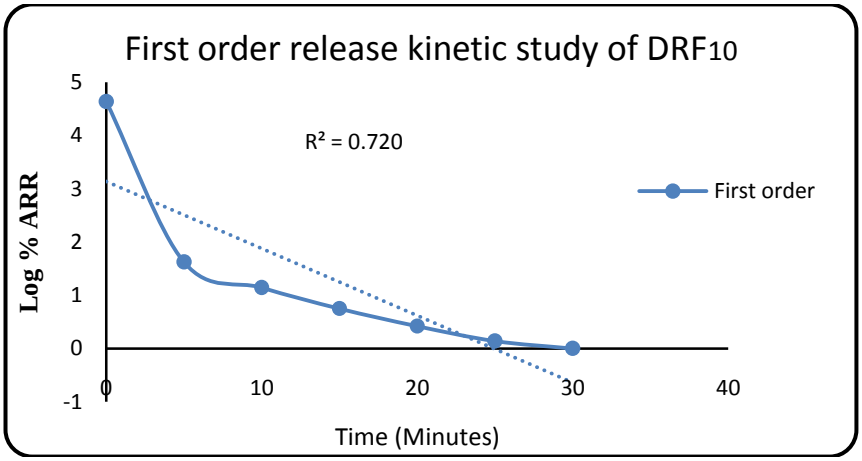

Fig. 7: First order release kinetic study of best formulation DRF10

Table 4: Regression values of invitro release kinetic study best formulation (DRF_{10})

Formulation	Zero-order (R^2value)	1st order (R^2value)	Remarks
DRF_{10}	0.9922	0.7204	Azero-order release kinetic model was followed

Stability studies

For accelerated stability testing, Dutasteride Orodispersible tablets' optimised formulation (DRF_{10}) was chosen. In vitro, drug release characteristics and physicochemical parameters did not significantly alter for the optimized formulation (DRF_{10}) of dutasteride orodispersible tablets. After 90 days of exposure to an accelerated stress situation, more than 90% of the medication was still present in the body according to in vitro dissolution experiments. As a result, the orodispersible Dutasteride (DRF_{10}) tablets were found to be stable for at least 3 months when kept in accelerated short-term storage conditions. The physicochemical parameters are represented whereas the in vitro drug release profile at accelerated conditions are represented in Figure8 and Table 5 respectively.

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Table 5: Comparative physicochemical properties of DRF_{10} at accelerated conditions (40 °C ± 2 °C/ 75% ± 5% RH)

TabletProperties	Initial	30 days after	Within 60 days	Within 90 days
Physical Surfacing	A smooth, concave surface that is light white and free of fractures	the same	the same	the same
Weight variation	4.25±0.56	4.18±0.46	4.15±0.25	4.10±0.31
Hardness	3.29±0.6	3.25±0.5	3.20±0.4	3.15±0.5
Friability	0.67±0.04	0.71±0.05	0.74±0.03	0.76±0.04
Disintegration time {D_t (Sec)}	78±0.42	75±0.45	72±0.51	70±0.55
Wetting time (Sec)	52±0.21	54±0.25	57±0.32	60±0.30
Drug content	99.41±1.3	98.36±1.2	96.43±1.1	94.25±1.2

All values are expressed as mean± SD; (n=3)

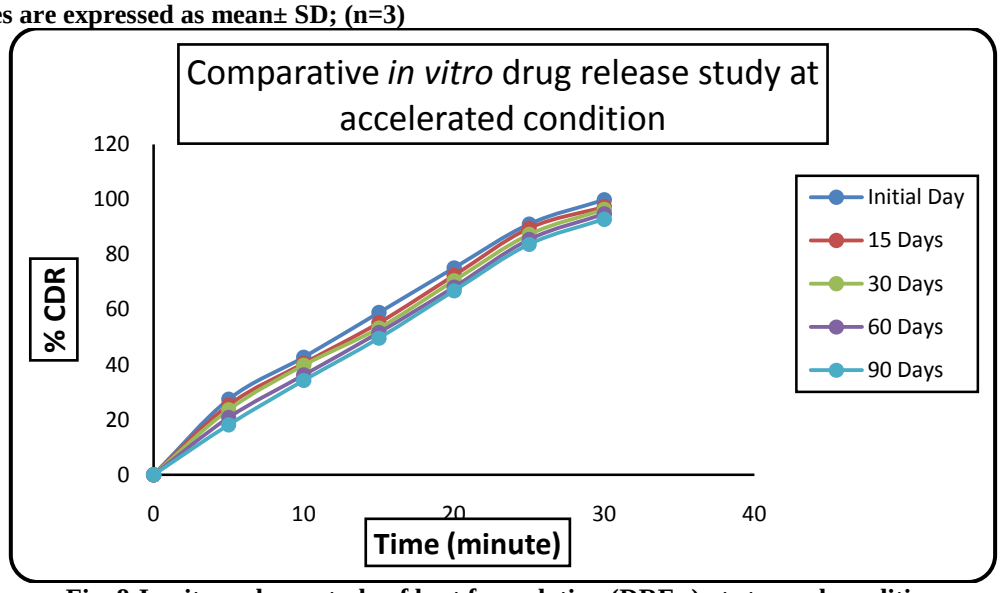

Fig. 8:In vitro release study of best formulation (DRF_{10}) at stressed condition

IV. CONCLUSION

This work created an effective method for producing orodispersible tablets of Dutasteride. The most difficult component of this experiment was evaluating the impact of the superdisintegrantsCrosscarmellose Sodium, Crospovidone, and Sodium Starch Glycolate on the in vitro release rate of an orodispersible Dutasteride tablet. The orodispersible medication delivery system has the potential to treat patients with enlarged prostates. fast drug release was achieved by circumventing fast metabolism. FTIR and DSC studies indicate that the drug and excipients exhibit stability within the formulation and demonstrate

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compatibility with each other. Wet granulation techniques were utilized to produce Dutasteride Orodispersible granules, and their analysis indicated that all precompression parameters exceeded acceptance criteria, confirming their excellent flow characteristics. Post-compression measurements indicate no unsatisfactory trends in any quality parameter, including thickness, hardness, friability, weight fluctuation, or crumbling. All formulations included lactose, a hydrophilic diluent, to improve the drug release profile. The medication is released at a rate exceeding 99% within 30 minutes, with the optimal initial release rate observed in Formulation DRF_{10}, which incorporates all three superdisintegrants at a concentration of 4% (2% Crosscarmellose, 1% Crosspovidone, and 1% Sodium Starch Glycolate). The combination of all three superdisintegrants resulted in a more advantageous medication release profile. Accelerated drug release may be attained by augmenting the concentration of superdisintegrants; however, this results in a compromise regarding the formulation's hardness and friability. The formulation DRF_{10} was chosen for drug release kinetics and mechanism testing because of its superior dissolution profile. Zero-order kinetics was seen for the Dutasteride orodispersible tablet due to its superior regression value. Stability studies were conducted in accordance with ICH guidelines, revealing that a specific DRF_{10} formulation could be maintained at 40°C/75% RH for a duration of three months with minimal changes to its physicochemical properties and drug release characteristics. The tablet's physical properties included friability, hardness, weight fluctuation, thickness, and medicine content. The enhanced fresh formulation (DRF_{10}) was evaluated in vitro both before to and during an accelerated stability assessment. The test has satisfied the requirements for stability. Dutasteride orodispersible tablets represent an innovative drug delivery technology since they facilitate rapid medication release via first-pass metabolism and are effective in treating acute conditions in males exhibiting signs of benign prostatic hyperplasia. Further clinical study is necessary to determine the efficacy of this technique for patients with enlarged prostate glands.

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