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Formulating, Optimizing and Evaluation of Dutasteride Loaded Insitu-Emulgel for Androgenetic Alopecia

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ABSTRACT
The current study aimed to develop a novel drug delivery system, Dutasteride loaded Insitu-emulgel, that enhances the drug's skin penetration and reduces the dosage required to provide the targeted effect. Additionally, it decreases adverse effects and improves patient compliance. Dutasteride is BCS class-II drug with high permeability and lower solubility. Dutasteride is an antiandrogen medication, that reduces the action of androgens on the follicle. These androgens are responsible for androgenic alopecia, i.e. it inhibits the enzyme 5α reductase which is responsible for transforming testosterone into dihydroxy testosterone and markedly suppresses serum DHT levels. Due to the antiandrogenic effects, it is used to treat a variety of dermatological conditions in which androgens, such as testosterone and dihydrotestosterone (DHT), play a role. So, dutasteride used in treatment of alopecia. Insitu-emulgel is more effective than any other topical preparation. The Insitu-emulgel also have the better loading capacity as compared to those of the niosomes and liposomes. Insitu-emulgel is easily removable from skin. Insitu-emulgel give controlled release of hydrophobic drug through skin. For the preparation of dutasteride Insitu-emulgel – Liquid paraffin used as a vehicle, span 20, tween 80 as emulsifier, Propylene glycol used as a penetration enhancer, triethanolamine as a neutralizer and ethanol used as a solvent. Then the emulsion was incorporated into gel base in 1:1 ratio to prepare Insitu-emulgel. Standard graph was drawn for Dutasteride and it was found that the solution shows linearity (R2=0.9987 in Phosphate buffer pH 6.8) and obey Beer's - Lambert's law with in the range of concentration used (5 µg/ml – 25 µg/ml). The Chemical compatibility study of Dutasteride with excipients was carried out using IR and FTIR Spectrometer. It revealed that there is no interaction between the drug and excipients. Central composite design (Design Expert, version 13, Stat Ease, Inc.) was used to build the formulation research design, and the formulation design was predicted and statistically assessed. The formulation variables of dutasteride loaded Insitu-emulgel containing 2 factors and evaluated at 2 levels. Amount of Liquid paraffin (A, 1 ml2 ml), amount of carbopol 940 (B, 150 mg-250 mg) as independent variables and drug release (R1), viscosity (R2) and drug content(R3) were selected as dependent responses. A total of 13 formulations were designed by the software with 2 centre points. The selected 13 formulations were evaluated for drug release, viscosity and drug content. The drug release was found to be in the range of 49.63% to70.61 %, viscosity was found to bein the range of from 4428 to 4803 cps and drug content was found to be in the range of 97.69% to 99.01%. By setting the criteria in the central composite design, it suggested the Optimized formulations. The design predicted the values of optimized Dutasteride loaded Insitu-emulgel formulation which was then formulated and evaluated and the predicted value was compared with actual value. The optimized Dutasteride loaded Insitu-emulgel formulations was white in colour, free from presence of particles, and showed good homogeneity and consistency with no phase separation. The pH of the optimized Insitu-emulgel was found to be 6.5±0.05 pH, which lies in the normal pH range of the skin (5.5-6.5). Thus, indicating the skin compatibility. The Viscosity and spreadability of Optimized dutasteride Insitu-emulgel formulation were found to be 4561±3.50 cps and 5.45±0.04 cm respectively, which indicates that the formulation is neither too runny nor too sticky and spread easily over the surface. Drug content in the optimized Insitu-emulgel formulation was determined by UV spectrophotometric method. The drug content was found to be 99.01±0.08%. In vitro Release profile of optimized formulation showed 59.02±0.002% release upto 6 hrs. This confirms that the drug released form the optimized Insitu-emulgel in a controlled manner. Based on the findings, it was determined that the Zero order release kinetics model had the highest correlation

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coefficient, R^2(0.9986),and was therefore the model that best fit the optimized dutaste ride loaded Insitu-emulgel. The fact that the value of "n" was calculated to be 0.1658 (0.45 < n < 0.89), suggests that the drug release from the polymeric matrix follows non-Fickian or anomalous transport. A dutasteride loaded Insitu-emulgel was developed for topical use. When compared to other traditional methods of administering topical medications, Insitu-emulgel seems to be a more sophisticated and efficient drug delivery technology. A large number of the formulations' components are extremely safe and stable for topical use. In order to treat androgenetic alopecia, the present study has succeeded in creating a topical Insitu-emulgel that is safe, economical, and efficient. To increase the effectiveness of treatment and patient compliance, more clinical research is being conducted in this area.

I. INTRODUCTION:

Skin diseases and pathological conditions affect people's mental and emotional well-being and quality of life [1,2]. As a result, the efficient prevention and treatment of skin diseases is a vital objective within contemporary medical practice. Notably, excessive hair loss, commonly referred to as alopecia, is one of the most frequently encountered dermatological issues [3, 4].Hair loss or alopecia is one of the most common problems in many societies and has serious economic and physiological consequences. Alopecia usually refers to the loss of hair on the scalp, but it can also affect other parts of the body [4].Alopecia, or hair loss, is frequently perceived as a normal part of aging, yet it can result in both psychological and pathological effects that are taken seriously by patients and medical practitioners alike.It is estimated that around 50% of men over 40 years old are affected by this condition, with a comparable number of women also experiencing hair loss. More than 90% of individuals, regardless of gender, wish to reverse or prevent their hair loss, often feeling a sense of frustration or helplessness, and they tend to be self-conscious about their condition [6].Alopecia Areata is characterized by the presence of round or oval areas where hair loss occurs without scarring. Although it is often associated with hair loss on the scalp, this condition can occur as part of alopecia (which can be temporary or permanent) or with complete hair loss (called alopecia totalis). In some cases, hair loss, known as alopecia universalis, can occur [5]. For many individuals, hair is a vital element of their overall appearance and a means of expressing their individuality. Hair also provides protective benefits; it helps to shield the scalp from the sun's harmful rays. Eyelashes and eyebrows are instrumental in keeping dust, dirt, and sweat at bay, preventing them from entering the eyes. The hair located in the nose and ears further assists in filtering out germs and other foreign substances. Additionally, body hair is important for maintaining body temperature: when temperatures drop, the hairs stand upright, trapping a layer of warm air close to the skin [7,8]. Each hair is made up of two main components: the hair shaft and the hair root. The hair shaft represents the portion of the hair that is visible above the skin's surface. In contrast, the hair root is located inside the skin and penetrates into the deeper layers. This root is surrounded by the hair follicle, a structure made of connective tissue that is also connected to the skin's outer layer and sebaceous glands[9]. Hydrocarbon side-chain amino acids, including glycine, and hydroxyl side-chain amino acids are found in comparatively considerable concentrations in human hair [10]. Once the hair has completely separated from the papilla, blood flow is stopped during the last resting phase, also referred to as the telogen phase. Over time, the hair is driven out of the skin and eventually falls off. The rest time might last for many months. The growth phase of the hair development cycle then begins anew when new hair cells begin to proliferate at the base of the "empty" hair follicle to generate a new hair[8 ,11]. Alopecia is the term used to describe the absence or loss of hair in a specific area. People of all ages and genders may be affected by this condition, which can be either localized or diffuse, temporary or persistent. Numerous factors might contribute to alopecia, a sign or symptom[12]. Alopecia areata is a chronic immune-mediated illness that affects children, adolescents, and adults of all ages. It often manifests as sudden, patchy hair loss on the scalp. Alopecia areata totals, or complete loss of scalp hair, and alopecia areata universalis, or loss of body hair, are uncommon presentations. A single episode or a trend of remission and recurrence may be experienced by patients[13, 14, 15]. Non inflammatory acute or chronic alopecia that often affects the whole scalp in children, adolescents, and adults of both sexes is called telogen effluvium. Psychological stress, chronic illness, pregnancy or postpartum, malnourishment, severe infection, endocrine disorders, metabolic disturbances, surgery, and medications like anticonvulsants, antidepressants, anticoagulants, oral contraceptive pills, and retinoids can all cause disruptions in the

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transition from the anagen phase to the telogen phase [16,17].

According to research, the frequency of AGA in the African population was 3.5% in women and 14.6% in males. AGA has a polygenetic and complex etiology. Although the route of inheritance is unknown, male AGA (MAGA) is evidently an androgen-dependent disorder with a hereditary predisposition. The function of androgens in female AGA (FAGA) remains unclear [18]. Genetic variations in the androgen receptor, namely the androgen receptor gene (AR) at the AR ⁄ ectodysplasin A2 receptor gene (EDA2R) locus, are responsible for male pattern hair loss. The location of the scalp affects the androgen sensitivity of hair follicles; male hair loss usually occurs in the bitemporal, mid-frontal, and vertex areas of the scalp. Notably, occipital hair follicles do not require androgen [19,20,21]. The X-chromosomal AR ⁄ EDA2R locus may be implicated in the pathophysiology of early-onset female pattern hair loss (FPHL), although the locus on chromosome 20p11 does not appear to be involved in FPHL. Estrogen may have a protective role in the age-related rise in FPHL, which is greatest in postmenopausal women. There is contradictory evidence about whether estrogen stimulates or inhibits the hair follicle [19,21,22]. In men, the vertex and frontotemporal areas are where hair loss is most noticeable, whereas in women, the frontal hairline is usually unaffected, and diffuse apical hair loss is seen as a broader anterior portion of the hair. While the Sinclair scale is used for women, the Hamilton–Norwood scale is utilized to evaluate the degree and severity of androgenetic alopecia in men [23, 24]. Although the transdermal route is preferred, there is a little catch: its purpose is to prevent foreign objects from entering the body[30,31]. When two or more liquids - which are frequently incompatible - combine, emulsions are produced. The oil and water phases are combined in this system using an emulsifying agent. Emulsions are stabilized by emulsifying agents. They penetrate well and are readily removed[32].

This allows for a significant amount of co-surfactant/surfactant mixing at the interface. The interface between the continuous and internal phases is stabilized by a suitable mixture of surfactants and/or co-surfactants[31]. A polymer that expands when exposed to fluid possibly inside its structure makes up a gel. The gel's rigidity is determined by the amount of fluid trapped inside it. These gels seem solid, but they are smooth and flowing. These may undergo significant physical deformation, changing from a solid to a liquid state[32].

The pharmaceutical industry frequently uses both types of emulgels to apply a range of drugs to the skin. One of its special qualities is that they may readily penetrate the skin. A classical emulsion, called emulgel, is created when a gelling agent is present in the water phase. To put it another way, several formulations are mixed to improve drug delivery; for instance, an emulgel is created when an emulsion and a conventional gel are combined. They are very well-liked by patients since they combine the qualities of gels and emulsions[33]. The medicate particles in an emulsion are solidified in the inside stage, which serves as a source of sedate from which the sedate travels via the outside stage to the skin, where it is digested. Because of its high permeability and poor solubility, emulgel is a better option for Class II drugs under the BCS classification [34].A variety of oils are used in the emulgel-making process. Mineral oils, vegetable oils, or fish liver oils were the most often used oils during the oil phase. Due of their local laxative properties, castor oil and non-biodegradable minerals are frequently utilized in oral preparations. As dietary supplements, other vegetable oils such arachis, cotton seed, and maize oil have been utilized [37, 38]. There are many types of oils listed below: Isopropyl palmitate, isopropyl stearate, isopropyl myristate, and liquid paraffin [40]. There are several penetration enhancers used, some of which are mentioned below: Lecithin, eucalyptus oil, urea, oleic acid, iso-propyl myristate, and menthol [41]. Techniques for optimization offer extensive knowledge as well as the capacity to investigate and defend ranges for formulation and processing components. It is now a helpful technique for quantifying a formulation that has been established qualitatively. To "optimize" anything means to make it as good, efficient, or useful as feasible [42-44].

II. METHODOLOGY

2.1. DRUG IDENTIFICATION

The following physical and chemical characteristics of the medication were tested as part of the early studies: Investigation of Dutasteride in Uv Spectrophotometric[61,62]

Stock solution of Dutasteride (100 µg mL^{-1}):

Accurately weighing 10 mg of the medication yielded the standard solution, which was then diluted with methanol in a 100 mL volumetric flask to create a stock solution of 100 µg mL-1 (stock solution1). In a 100 ml standard

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flask, take 10 ml of the previously mentioned stock solution I and fill it to the full capacity with a pH 6.8 phosphate buffer solution (stock solution II). Further dilutions of the standard solution were made using this stock solution.

Determining the maximum absorption wavelength (λmax) of dutasteride:

A number of 10 ml volumetric flasks were filled with aliquots of the dutasteride stock solution and phosphate buffer 6.8 was added to the volume to create concentrations ranging from 5 to 25 µg mL-1. 242 nm was chosen as the λmax from the UV absorption spectra, which were acquired by scanning the pure drug solutions in the 200–400 nm range. This allowed for the preparation of the calibration curve by measuring the absorbance of the mentioned solutions.

Calibration curve

The calibration curve was created by diluting the standard stock solution with phosphate buffer and plotting it within the concentration range of 5–25µg mL–1. At 242 nm, the absorbance was measured in relation to the matching solvent blank. To determine the calibration curve and regression coefficient (r2), the linearity of the plot between absorbance and drug concentration in the concentration range of 5–25µg mL-1 was computed.

2.2. DRUG AND EXCIPIENT COMPATABILITY STUDY

Compatibility tests are performed to ascertain whether there is any interaction between the drug and excipients. This was done in order to detect any changes in the drug's chemical composition after it was mixed with excipients. The method that will be employed to investigate the compatibility of drugs and polymers is an infrared spectroscopy examination.

Fourier Transform Infra-Red spectroscopic (FT-IR) studies:

A simple technique for identifying interactions between several APIs or between the API and excipients is IR, FT-IR. IR, FT-IR Spectroscopy was used to investigate the drug (dutasteride), polymers (Span20, Tween 80, Propylene glycol, Carbopol 940), and physical mixing of the drug with the polymers in the 400–4000 cm-1 range. In order to determine whether any functional peaks had shifted or whether any new functional peaks had appeared or vanished, the resulting spectra were compared and interpreted with the standard peaks.

2.3. OPTIMIZATION OF DUTASTERIDE LOADED INSITU-EMULGEL USING CENTRAL COMPOSITE DESIGN [62, 63]:

Drug delivery system development and optimization frequently make use of RSM as an experimental design technique [63]. With comparatively few tests, several independent variables may be studied simultaneously via the central composite design (CCD) [64]. Therefore, in order to improve the formulation and systematically examine the impact of independent and dependent factors, a central composite design response surface methodology (CCD-RSM) was employed.

The RSM CCD tool was used to formulate the experimental design, which was created with Design-Expert 13.0 software. To statistically optimize the formulation components and assess the main, interaction, and quadratic impacts on the independent factors, a central composite statistical design was created. Design Expert (Version 13) was utilized to investigate quadratic response surfaces and build second order polynomial models using 2 factors, 2 level central composite design. A matrix with 2 factors, 2 level, and 10 runs was chosen for the optimization investigation. A collection of points located at the midpoint of each edge and the repeated center point of a multidimensional cube make up the experimental design. Table 6 lists the independent and dependent variables.

The polynomial equation generated by this experimental design is as follows,

$$Y = \beta 0 + \beta 1X1 + \beta 2X2 + \beta 12X1X2 + \beta 11X12 + \beta 22X22.$$

Where, Y is the dependent variable, β0 is the intercept, β1 to β33 are the regression coefficient and X1, X2 and X3 are the independent variables selected from preliminary experiments. The experimental design is summarized in Table 6.

Optimization validation and data analysis:

The formulation of DUT-Insitu-emulgel was optimized through the use of "central composite design" and "design expert software-version 13," which consists of two components and two levels. Castor oil (A, −1 = 1 ml and +1 = 2 ml) and carbopol 940 concentration (B, −1 = 150 mg and +1 = 250 mg) were the independent variables chosen. Drug release (R1), viscosity (R2), and drug content (R3) were the dependent variables. Table 1 presents a summary of the experiment design.

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Using Design Expert software, the polynomial equation and ANOVA were statistically validated. To determine the prediction error, the experimental values obtained from the answers were compared quantitatively with the expected values.

TABLE 1: SUMMARY OF EXPERIMENTAL DESIGN

INDEPENDENT VARIABLES	UNITS	LEVELS		
		Low (-1)	Medium (0)	High (+1)
Liquid paraffin (A)	ml	1	1.5	2
Carbopol 940 (B)	mg	150	200	250
DEPENDENT VARIABLES	**UNITS**	**CONSTRAINTS**		
drug release (r1)	%	Minimize		
Viscosity (r2)	cps	In range		
drug content(r3)	%	Maximize		

2.4. FORMULATION OF DUTSTERIDE LOADED INSITU - EMULGEL [65-68]:

❖ In situ- emulgel was prepared by the hot method.

STEP 1: FORMULATION OF GEL BASE.

The gel was prepared by dispersing gelling agent in water under magnetic stirrer, and the dispersion was cooled and left overnight.

STEP 2: FORMULATION OF DUTASTERIDE EMULSION.

The liquid paraffin is an oil phase, and the tween-80 emulsifier was dissolved in water to create the aqueous phase. Polyethylene glycol (PEG) and drug that had been dissolved in ethanol were introduced to the oil phase. The oily and aqueous phases were heated to 70° to 80°C separately. After that, the oily phase was added to the aqueous phase and stirred constantly until the mixture cooled to room temperature.

STEP 3: INCORPORATION OF THE EMULSION INTO GEL BASE.

The obtained emulsion was incorporated into the gel in 1:1 ratio with gentle stirring to obtain the Insitu - emulgel.

TABLE 2: FORMULATION OF DUTASTERIDE LOADED INSITU – EMULGEL(CCD)

S.NO	INGREDIENTS	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13
1.	Dutasteride (mg)	50	50	50	50	50	50	50	50	50	50	50	50	50
2.	Liquid paraffin (ml)	1.5	1.5	0.8	1.5	1	1.5	2	1.5	2	1	1.5	2.2	1.5
3.	Span 20 (ml)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
4.	Tween 80 (ml)	1	1	1	1	1	1	1	1	1	1	1	1	1
5.	Ethanol (ml)	2	2	2	2	2	2	2	2	2	2	2	2	2
6.	Propylene glycol (ml)	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
7.	Carbopol940 (mg)	200	200	200	129	150	271	150	200	250	250	200	200	200
8.	Triethanolamine (ml)	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
9.	Dis. water (ml)	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

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2.5. CHARACTERIZATION OF DUTASTERIDE LOADED INSITU-EMULGEL:

Physical appearance

The prepared Insitu - emulgel formulations were inspected visually for their color, homogeneity, consistency and pH.

pH measurement

The pH values of 1% aqueous solutions of the prepared gellified emulsion were measured by a pH meter (Digital pH meter).

Globule size measurement [69]

Globule size of Insitu-emulgel formulation was measured by using optical microscope.

Photomicrography [70]

Morphology of emulsion was studied under light microscope. Optimized batches of the Insitu-emulgel were viewed under light microscope to study their shape. The emulgel was suitably diluted, mounted on glass slide and viewed by light microscope under magnification of 40 X.

Spreadability [71]

The efficacy of Insitu-emulgel depends on its spreading. The spreading helps in the application of gel to the skin, therefore the prepared Insitu-emulgel should have good spreadability. The parallel- plate method was used to measure the spreadability, A required amount of gel was placed within a circle of 1cm diameter which is pre-marked on a glass plate, above which another glass plate was placed, to estimate the spreadability. A weight of 500 gm was permitted to rest on the upper glass plate for 5 min. The increase within the diameter spreading was noted.

Rheological Study [69]

The viscosity of the Insitu-emulgel was determined using a Brookfield Viscometer with spindle 64. The viscosity of the formulations to be determined was added to the beaker and was allowed to settle down for 30 minutes at the assay temperature (25° ± 1°C) before the measurement was taken. Spindle was lowered perpendicularly to the center of the gel; taking care that spindle does not touch the bottom of the beaker and rotated at a speed of 30 rpm for 10 min. The viscosity reading was noted down. The average of three readings was taken in 10 minutes was noted as the viscosity of gel.

Swelling Index [69]

To determine the swelling index of prepared topical Insitu-emulgel, 1 gm of gel is taken on porous aluminum foil and then placed separately in a 50 ml beaker containing 10 ml 0.1N NaOH. Then samples were removed from beakers at different time intervals and put it on dry place for some time after it reweighed. Swelling index is calculated as follows:

Swelling Index (SW) % = [(Wt. –Wo) / Wo] × 100.

Where,

(SW) % = Equilibrium percent swelling,

Wo = Original weight of Insitu-emulgel at zero-time, Wt. = Weight of swollen Insitu-emulgel after time t.

Drug Content Determination:

Weigh specific quantity of gel containing 10 mg of drug and add sufficient qty of methanol and diluted with phosphate buffer pH 6.8 and stir the solution for 2 hours on a magnetic stirrer. The resulting solution was filtered using Whatman filter paper, and after appropriate dilution, the samples were analyzed spectrophotometrically at 242 nm against blank using UV- Visible spectrophotometer.

2.6. In Vitro Release Study:

In vitro drug release studies were carried out using Franz diffusion cell. 0.5 g of gel was applied on egg membrane as donor compartment. Phosphate buffer pH 6.8 was placed in the receptor compartment as the dissolution medium. The whole assembly was place on magnetic stirrer with thermostat maintained at 37^{o}C. Samples were collected regular time interval and sink conditions were maintained by replacing with new buffer solution. Collected samples are analyzed at 242 nm using UV spectrophotometer.

III. RESULTS AND DISCUSSION

I. PREFORMULATION STUDIES

A) SPECTROMETRIC IDENTIFICATION OF DUTASTERIDE: ESTIMATION OF ABSORPTION MAXIMA (λ-max):

The drug's diluted concentration (10µg/ml) in phosphate buffer was scanned between 200 and 400 nm using a double beam UV-visible spectrophotometer to measure the absorption maximum (λ-max) of dutasteride. The observed spectra indicated that the dutasteride's

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absorption maximum (λ-max) was 242 nm.

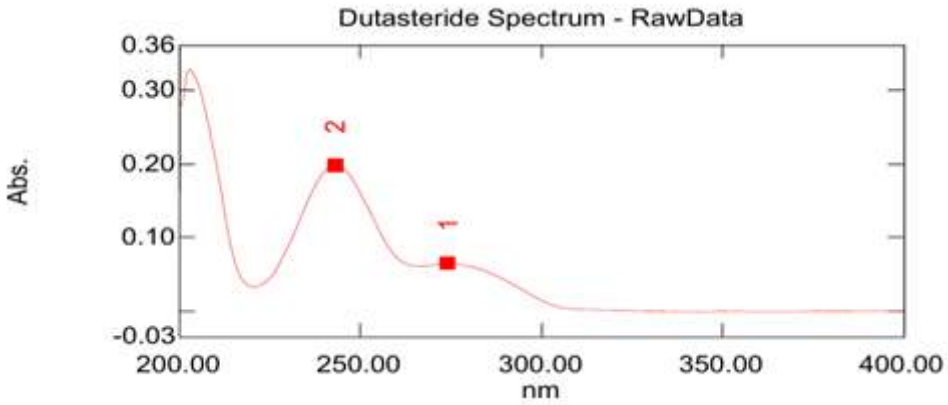

FIG. 9: Estimation of absorption maxima (λ-max)

CALIBRATION OF DUTASTERIDE IN PHOSPHATE BUFFER PH 6.8:

Phosphate buffer pH 6.8 was used to create the dutasteride standard calibration curve. At λ-max of 242 nm, the absorbance was measured. A correlation coefficient of 0.9986 was discovered. In the concentration range of 5–25µg/ml, dutasteride complies with the Beer–Lambert law. Table 6 showed the calibration curve of dutasteride in phosphate buffer at pH 6.8.

TABLE 8: ABSORBANCE OF DUTASTERIDE IN PHOSPHATE BUFFER PH 6.8.

S.NO	CONCENTRATION (µg/ml)	ABSORBANCE (nm)
1.	5	0.121
2.	10	0.215
3.	15	0.319
4.	20	0.421
5.	25	0.543
6.	30	0.658

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CALIBRATION CURVE OF DUTASTERIDE:

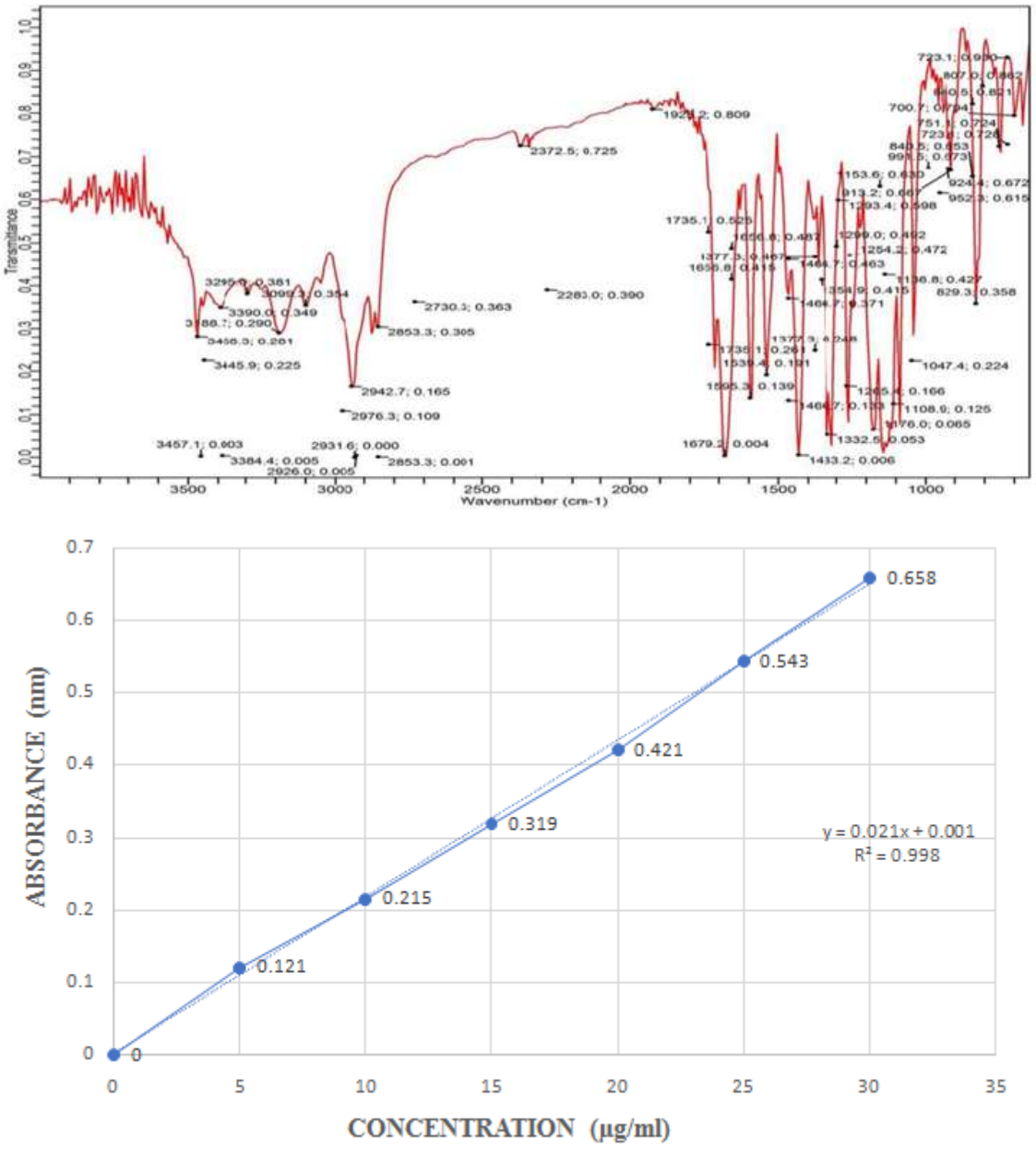

FIG. 10: CALIBRATION CURVE OF DUTASTERIDE

II. DRUG-EXCIPIENT COMPATABILITY STUDIES USING FT-IR SPECTROSCOPY:

The IR, FT-IR Study was conducted to confirm the compatibility between drug and excipients to identify the possible interactions. FT-IR Spectrum was performed for pure drug, (dutasteride), excipients and physical mixture of drug and excipients.

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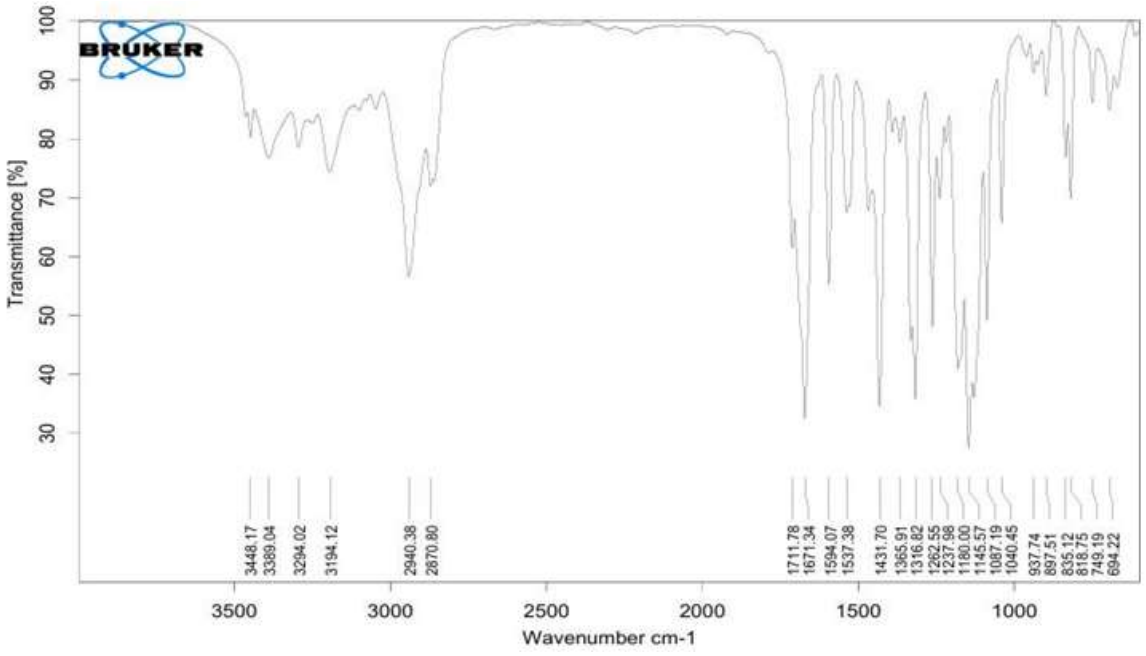
Dutasteride:
IR spectra of Dutasteride:
FT-IR spectra of Dutasteride:

FIG. 11: IR, FT- IR spectra of Dutasteride Table 9: Characteristic peaks of dutasteride

S. No	Wavenumber(cm-1)	Functionalgroup
1.	3294	2^{o}aminestretching
2.	2940	AromaticC-Hstretching
3.	1711	C=Ostretching
4.	1671	C=Cstretching
5.	1594	N-Hstretching
6.	1431	CH_2stretching
7.	1316	C-Nstretching
8.	1145	C-Fstretching



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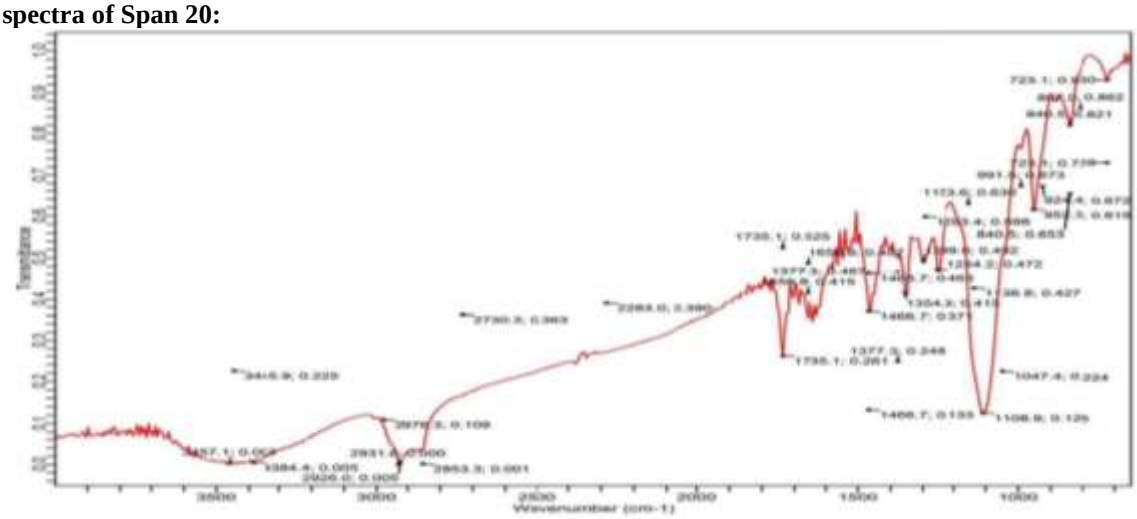
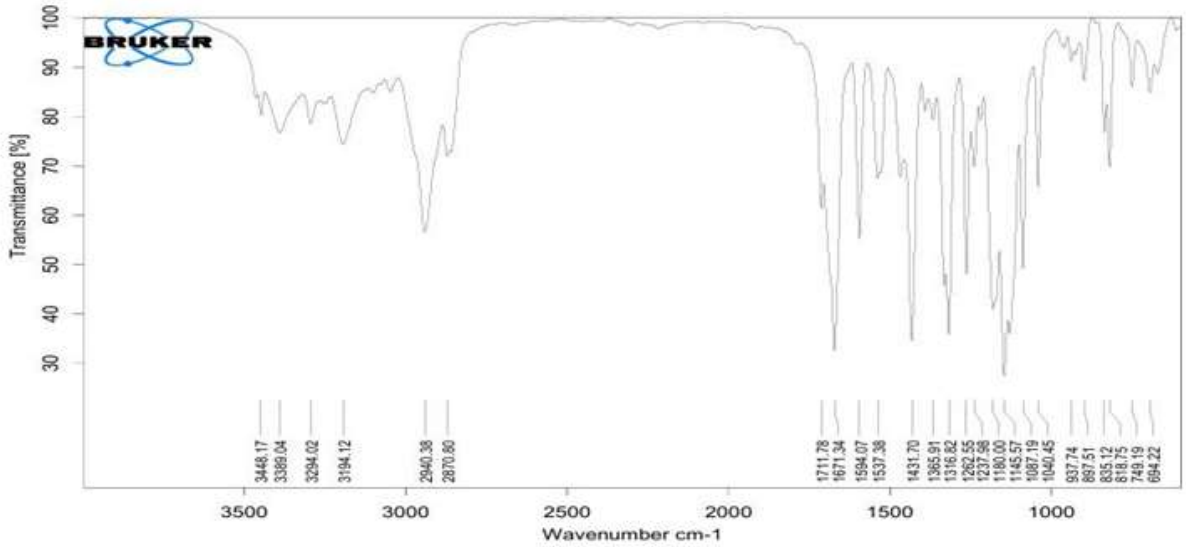
Span 20:

IR spectra of Span 20:



FT-IR spectra of Span 20:



\FIG. 12: FT-IR spectra of Span 20

Table 10: Characteristic peaks of Span 20:

S. No	Wave number (cm-1)	Functional group
1.	3395	O-H stretching
2.	2869	Aliphatic C-H stretching
3.	1735	C=O stretching
4.	1460	CH2 bending
5.	1108	C-O-C stretching

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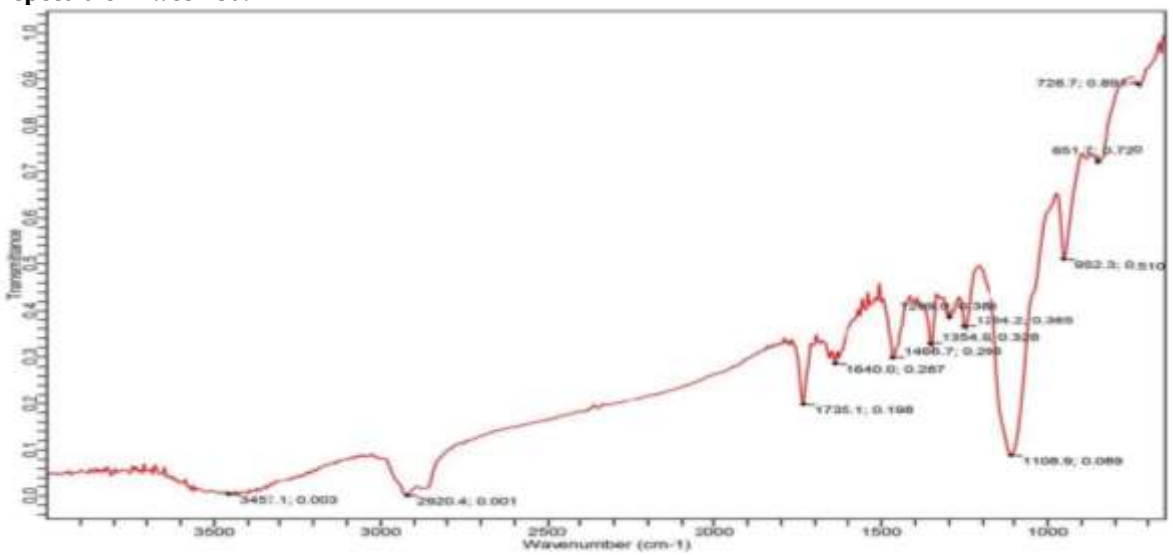
Tween 80:

IR spectra of Tween 80:



FT-IR spectra of Tween 80:

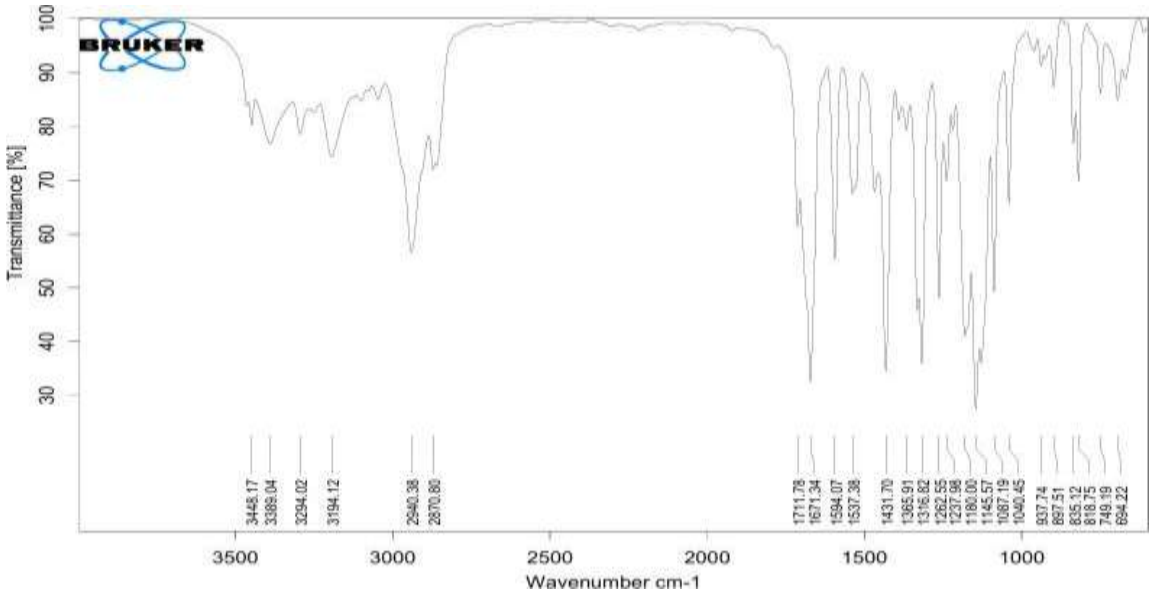


FIG. 13: IR, FT-IR spectrum of Tween 80

Table 11: Characteristic peaks of Tween 80

S. No	Wave number (cm-1)	Functional group
1.	3398	O-H stretching
2.	2924	Aliphatic C-H stretching
3.	1740	C=O stretching
4.	1463	CH2 bending vibration
5.	1173	C-O-C stretching
6.	1076	Ester stretching

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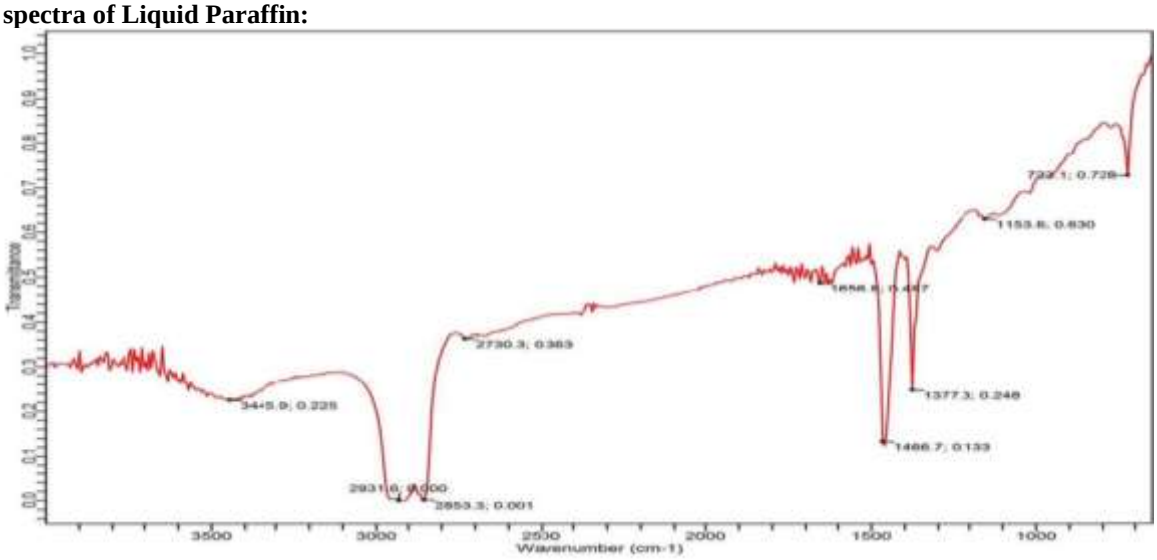
Liquid Paraffin:

IR spectra of Liquid Paraffin:



FT-IR spectra of Liquid Paraffin:

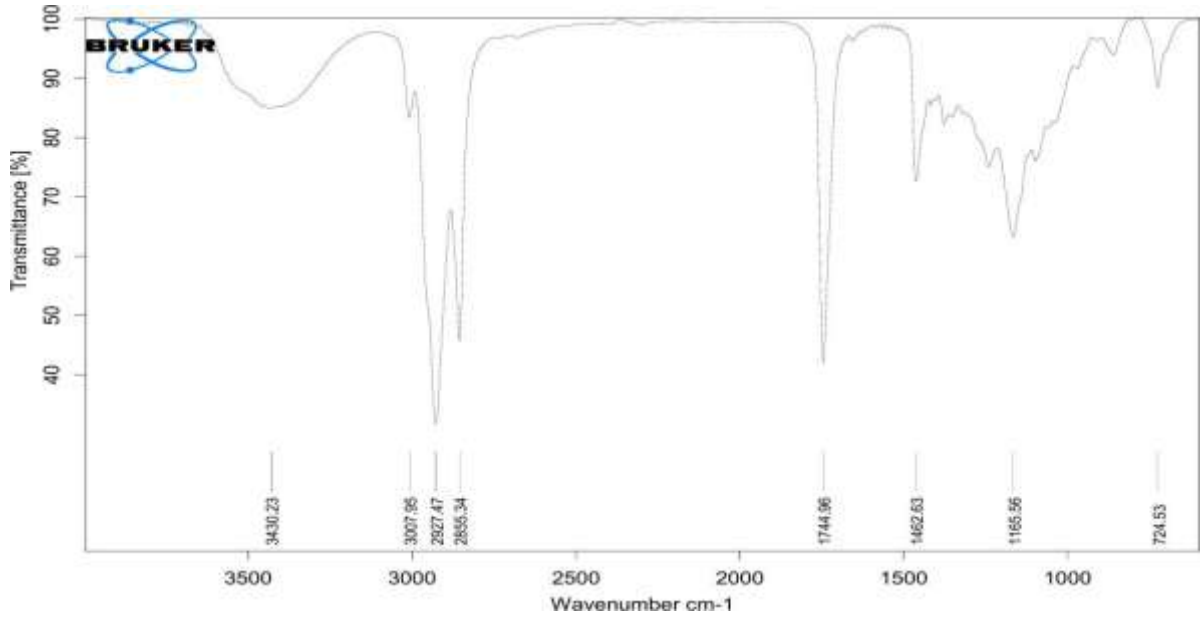


FIG. 14: FT-IR spectrum of Liquid Paraffin

Table 12: Characteristic peaks of Liquid Paraffin

S. No	Wave number (cm-1)	Functional group
1.	3417	O-H alcohols
2.	2931	C-H alkanes
3.	1465	C-C alkenes
4.	1373	Alkanes
5.	725	Alkyl halides

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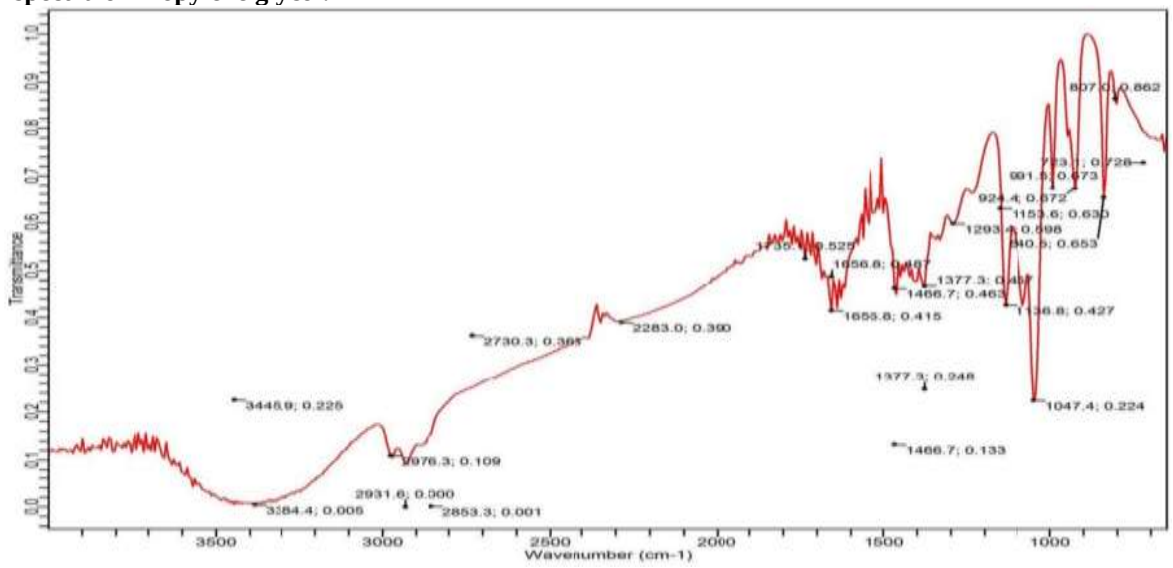
Propylene glycol:

IR spectra of Propylene glycol:



FT-IR spectra of Propylene glycol:

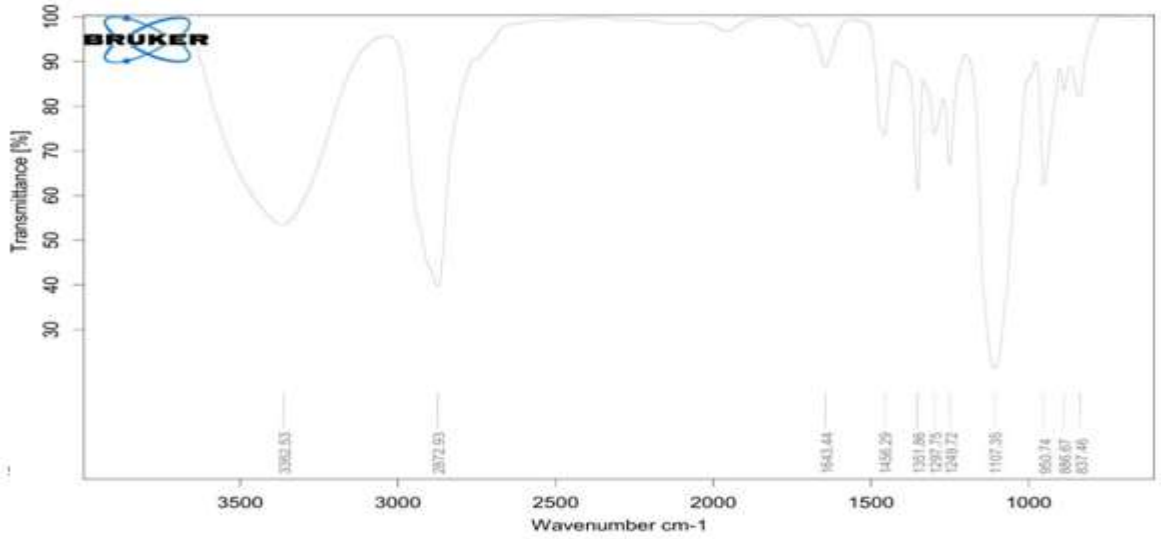


FIG. 15: FT-IR spectrum of Propylene glycol

Table 13: Characteristic peaks of Propylene glycol

S. No	Wave number (cm-1)	Functional group
1.	3362	O-H stretching
2.	2872	Aliphatic C-H stretching
3.	1456	CH2 bending
4.	1107	C-O-C stretching

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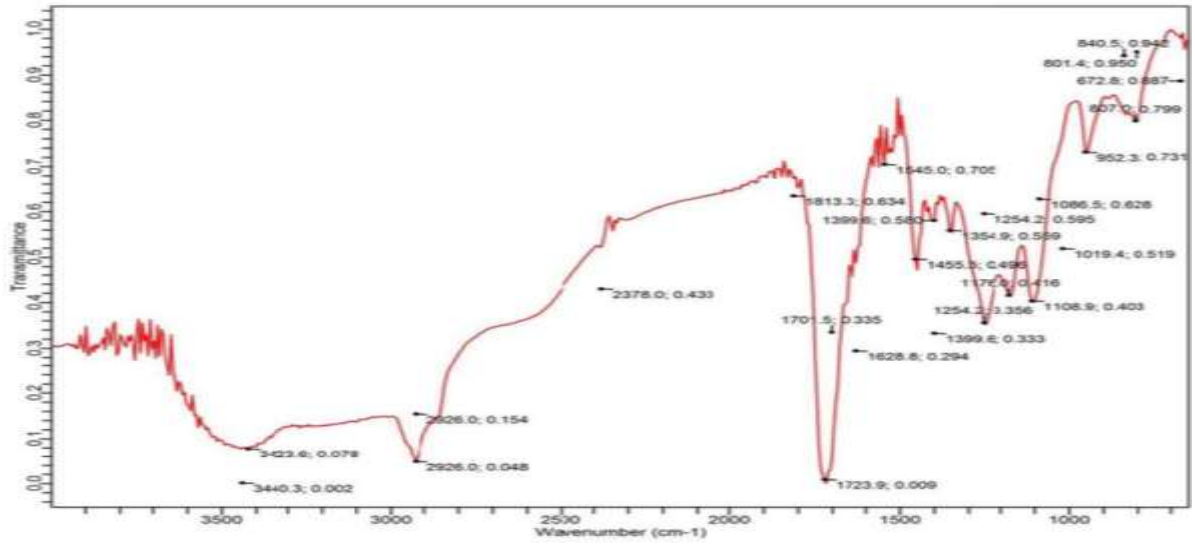
Carbopol 940:

IR spectra of Carbopol 940:



FT-IR spectra of Carbopol 940:

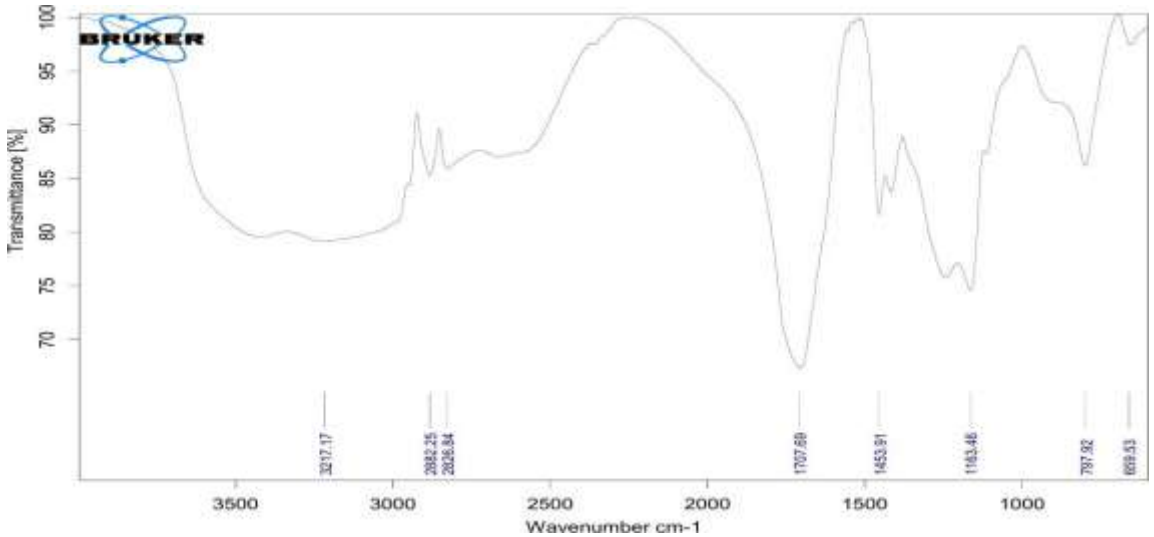


FIG. 16: FT- IR spectra of Carbopol 940

Table 14: Characteristic peaks of Carbopol 940

S. No	Wave number (cm-1)	Functional group
1.	3524	O-H Stretching
2.	3130	C=C Aromatic Stretching
3.	2927	Aliphatic C-H Stretching
4.	1704	C=O Stretching
5.	1455	C-F Stretching
6.	1161	Ester sharp band

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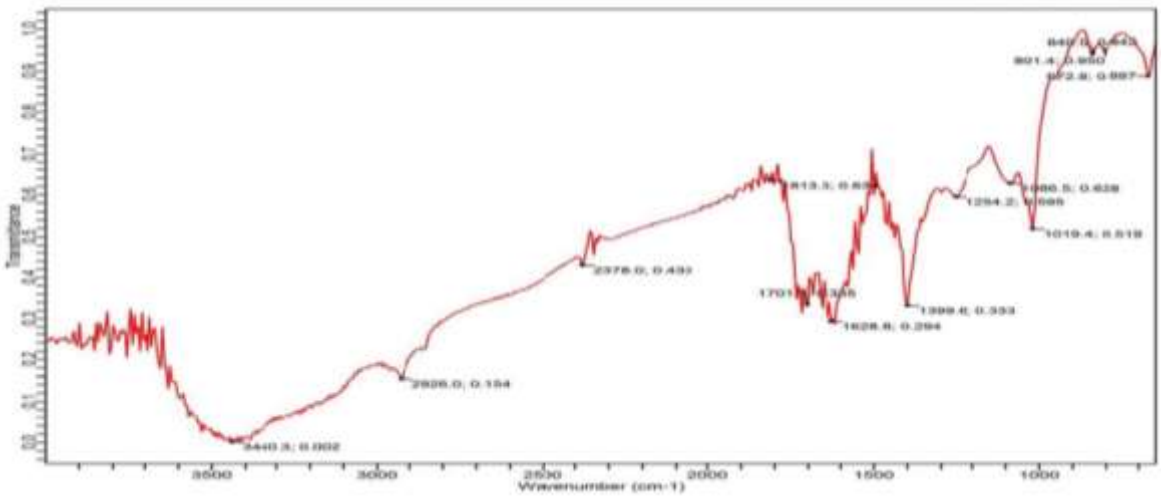
Physical mixture:

IR spectra of physical mixture:



FT-IR spectra of physical mixture:

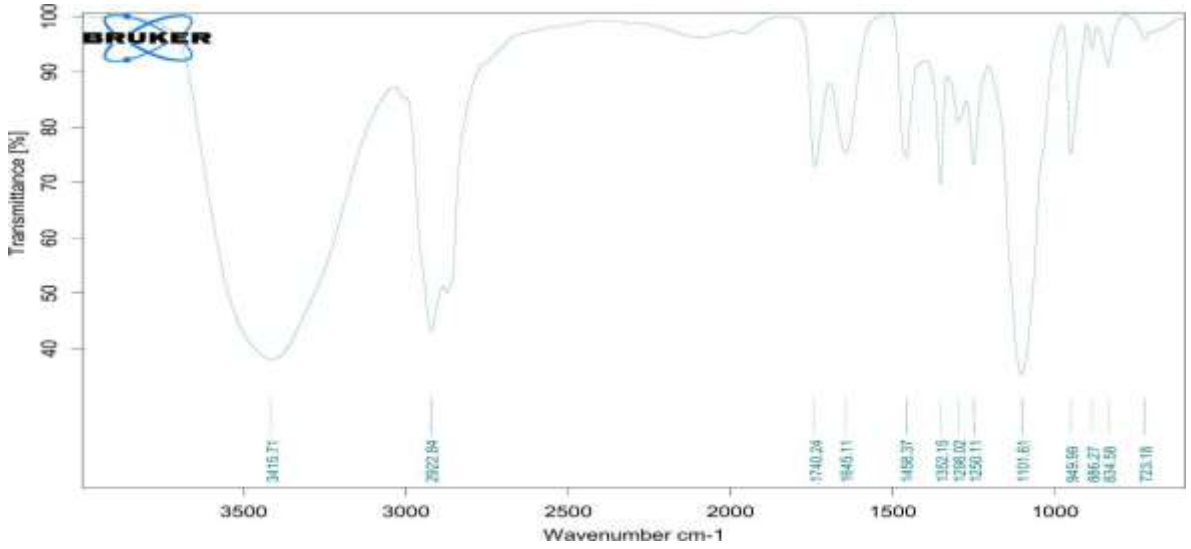


FIG. 17: FT-IR spectra of physical mixture

Table 15: Characteristic peaks of physical mixture

S. No	Wave number (cm-1)	Functional group
1.	3416	O-H stretching
2.	2926	Aromatic C-H stretching
3.	1741	C=O stretching
4.	1643	C=C stretching
5.	1455	CH2 bending
6.	1253	C-O-C stretching
7.	1102	Ester stretching
8.	781	C-Cl Stretching

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III. CENTRAL COMPOSITE DESIGN:

The Dutasteride loaded Insitu - emulgel in this study was examined at two levels and its formulation variables were optimized using a CCD that had two parameters. Requirements for dependent responses were drug release (R1), viscosity (R2), drug content (R3), the amount of liquid paraffin (A), amount of carbopol 940 (B). Table-16 lists the independent components and range levels that were employed in the investigation. A layout of the design is presented in Table-16 and the trials were planned with Design Expert software (Version 13, Stat-Ease Inc.). The program generated 13 different formulas with two center points.

TABLE 16: INDEPENDENT VARIABLES USED IN CCD

INDEPENDENTVARIABLES	UNITS	LEVELS		
		Low (-1)	Medium (0)	High (+1)
Liquid paraffin (A)	ml	1	1.5	2
Carbopol 940 (B)	mg	150	200	250

TABLE 17: ACTUAL DESIGN OF CENTRAL COMPOSITE DESIGN FOR DUTASTERIDE INSITU-EMULGEL

Run	Factor 1	Factor 2	Response 1	Response 2	Response 3
	A: Liquid paraffin (ml)	B: Carbopol 940 (mg)	Drug Release %	Viscosity cps	Drug content %
1	1.5	200	68.16	4519	97.87
2	1.5	200	68.95	4511	97.78
3	0.8	200	67.56	4530	97.82
4	1.5	129	49.63	4462	98.96
5	1	150	56.52	4428	98.53
6	1.5	271	63.03	4803	98.39
7	2	150	59.02	4561	99.01
8	1.5	200	68.98	4528	97.95
9	2	250	67.11	4721	98.42
10	1	250	67.67	4698	97.89
11	1.5	200	69.11	4520	97.82
12	2.2	200	70.61	4635	98.56
13	1.5	200	69.12	4526	97.69

Table 18: Design Summary (Design Model: Quadratic; **Type**: Numeric)

Factor	Name	Units	Min	Max	Coded		Mean	Std.Dev.
					Low	High		
A	Liquid paraffin	ml	0.80	2.20	-1	+1	1.50	0.4062
B	Carbopol940	mg	129.00	271.00	-1	+1	200.00	40.91

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ANOVA for Response Surface Quadratic Model

Table 23: Analysis of variance table [Partial sum of squares – Type III]

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	471.23	5	94.25	455.84	< 0.0001	**significant**
A-Liquid paraffin	4.87	1	4.87	23.55	0.0019	
B-Carbopol 940	182.31	1	182.31	881.77	< 0.0001	
AB	2.34	1	2.34	11.32	0.0120	
A^2	0.0292	1	0.0292	0.1412	0.7182	
B^2	276.38	1	276.38	1336.75	< 0.0001	
Residual	1.45	7	0.2068			
Lack of Fit	0.8047	3	0.2682	1.67	0.3092	Not significant
Pure Error	0.6425	4	0.1606			
Cor Total	472.67	12				

The **Model F-value** of 455.84 implies the model is significant. There is only a 0.01% chance that an F-value this large could occur due to noise.

P-values less than 0.0500 indicate model terms are significant. In this case A, B, AB, B^2 are significant model terms. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model.

The **Lack of Fit F-value** of 1.67 implies the Lack of Fit is not significant relative to the pure error. There is a 30.92% chance that a Lack of Fit F-value this large could occur due to noise. Non-significant lack of fit is good -- we want the model to fit.

Final Equation in Terms of Coded Factors:

Table 26: Final Equation in Terms of Coded Factors

Drug Release	=
+68.86	
+0.7841	A
+4.76	B
-0.7650	AB
+0.0658	A^2
-6.26	B^2

The equation in terms of coded factors can be used to make predictions about the response for given levels of each factor. By default, the high levels of the factors are coded as +1 and the low levels are coded as -1. The coded equation is useful for identifying the relative impact of the factors by comparing the factor coefficients.

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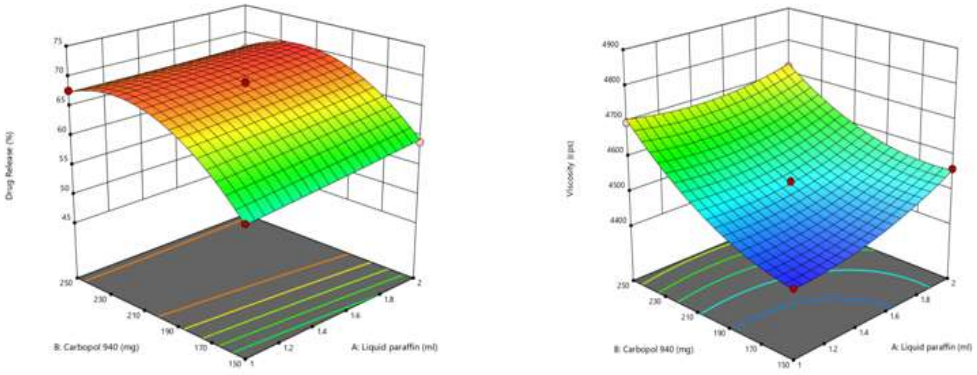
Final Equation in Terms of Actual Factors:

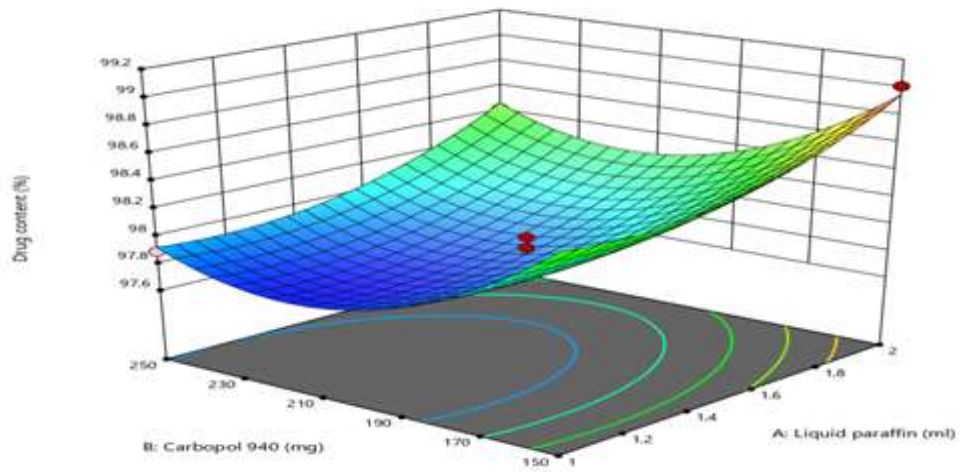
Table 27: Final Equation in Terms of Actual Factors

Drug Release	=
-61.29841	
+6.89884	Liquid paraffin
+1.14285	Carbopol 940
-0.030600	Liquid paraffin * Carbopol 940
+0.263115	Liquid paraffin²
-0.002504	Carbopol 940²

The equation in terms of actual factors can be used to make predictions about the response for given levels of each factor. Here, the levels should be specified in the original units for each factor. This equation should not be used to determine the relative impact of each factor because the coefficients are scaled to accommodate the units of each factor and the intercept is not at the center of the design space



3D



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IV. CHARACTERIZATION OF DUTASTERIDE LOADED INSITU-EMULGEL:

PHYSICAL APPEARANCE AND HOMOGENEITY:

The physical appearance and homogeneity of the dutasteride loaded Insitu-emulgel were observed visually and the results were shown in the table.

TABLE 48: PHYSICAL CHARACTERS OF OPTIMIZED FORMULATION

S.NO	PHYSICAL CHARACTERS	DUTASTERIDE LOADED INSITU-EMULGEL
1.	Colour	White
2.	Homogeneity	Excellent
3.	Consistency	Excellent
4.	Phase separation	None

MEASUREMENT OF pH:

TABLE 49: PH OF OPTIMIZED FORMULATION

FORMULATION	pH	AVERAGE
Optimized DUT-Insitu-emulgel formulation	6.5	6.5±0.05
	6.6	
	6.5	

A pH meter was used to measure the pH after dipping into the gel formulation and letting it equilibrate. As shown in the table, the gel's pH was 6.5±0.05, which is within the skin's typical pH range and suggests skin compatibility.

GLOBULE SIZE MEASUREMENT:

Globule size measurement by optical microscopy
Calibrationof eyepiece micrometer: One division of stage micrometer = 10µm
1divisionofstagecoincidewiththe3divisionofeyepiecemicrometer.
Onedivisionofeyepiece micrometer =1\3 x 10µm = 3.33 µm.

TABLE 50: GLOBULE SIZE MEASUREMENT

S. No	No of eyepiece division x No of eyepiece calibration	Frequency (n)
1.	1×3.33 = 3.33	11
2.	2×3.33 = 6.66	35
3.	3×3.33 = 9.99	56
4.	4×3.33 = 13.32	59
5.	5×3.33 = 16.65	49
6.	6×3.33 = 17.78	37
7.	7×3.33 = 27.31	28
8.	8×3.33 = 26.64	25
Avg. globule size = 15.21µm		

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PHOTOMICROGRAPHY:

A light microscope was used to analyze the suitably diluted emulsions of the optimized batches at 40X magnification (Fig. 24). The photomicrograph showed globules of emulsion that were nearly spherical. This study offers an overview of the emulsion formation process and the efficacy of the used technique, considering the fact that it does not provide a specific size estimate.

FIG. 24: 40X MAGNIFICATION OF INSITU-EMULGEL

SPREADABILITY:

TABLE 51: SPREADABILITY OF OPTIMIZED FORMULATION

FORMULATION	SPREADABILITY (Cm)	AVERAGE
Optimized DUT-Insitu-emulgel formulation	5.41	5.45±0.04
	5.49	
	5.45	

The spread ability of optimized formulation was found to be 5.45±0.04cm, which shows that formulation has a good spread ability.

MEASUREMENT OF VISCOSITY:

TABLE 52: VISCOSITY OF OPTIMIZED FORMULATION

FORMULATION	VISCOSITY (cps)	AVERAGE (cps)
Optimized DUT-Insitu-emulgel formulation	4561	4561±3.50
	4558	
	4565	

The Viscosity of Optimized Formulation was found to be 4561±3.50 cps.

SWELLING INDEX:

TABLE 53: SWELLING INDEX OF OPTIMIZED FORMULATION

FORMULATION	SWELLING INDEX (%)	AVERAGE (%)
Optimized DUT-Insitu-emulgel formulation	27.59	25.85±1.74
	25.85	
	24.11	

The swelling index of optimized formulation was found to be 25.85 ±1.74 %

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DETERMINATION OF DRUG CONTENT IN GEL:

TABLE 54: DRUG CONTENT OF OPTIMIZED FORMULATION

S.NO	FORMULATION	DRUG CONTENT (%)
1.	F1	97.87±0.05
2.	F2	97.78±0.02
3.	F3	97.82±0.03
4.	F4	98.69±0.01
5.	F5	98.53±0.06
6.	F6	98.39±0.05
7.	F7	99.01±0.08
8.	F8	97.95±0.02
9.	F9	98.42±0.01
10.	F10	97.89±0.03
11.	F11	97.82±0.05
12.	F12	98.56±0.03
13.	F13	97.69±0.07

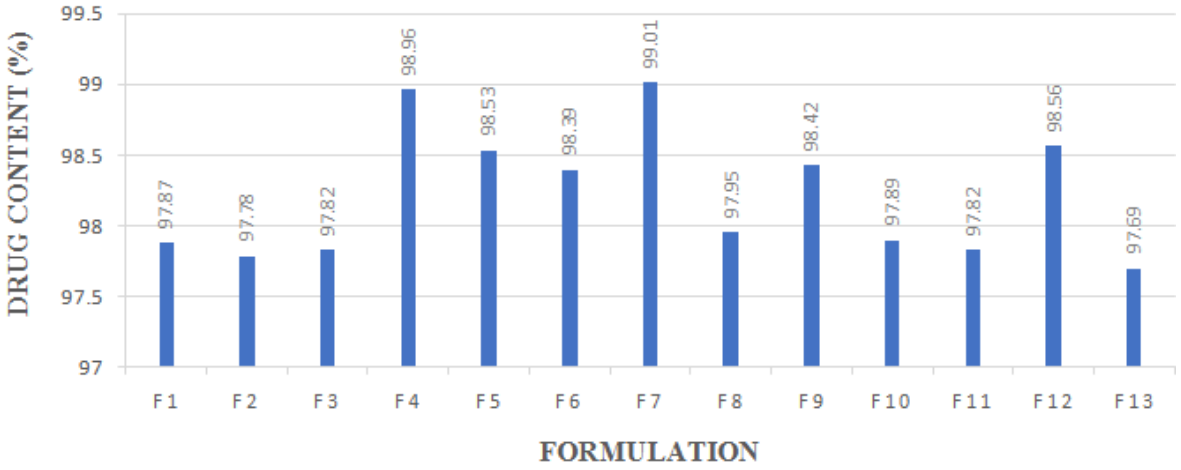

FIG. 25: DRUG CONTENT OF INSITU-EMULGEL

INFERENCE: The drug content of optimized formulation was found to be 99.01±0.08%.

V. IN VITRO DRUG DIFFUSION STUDIES:

The Franz diffusion cell equipment was used to conduct in vitro drug diffusion tests for the improved Dutasteride loaded Insitu-emulgel formulation across egg membrane in phosphate buffer pH 6.8. The graph was plotted against Time (hrs) on X axis vs Cumulative % drug release on Y axis.

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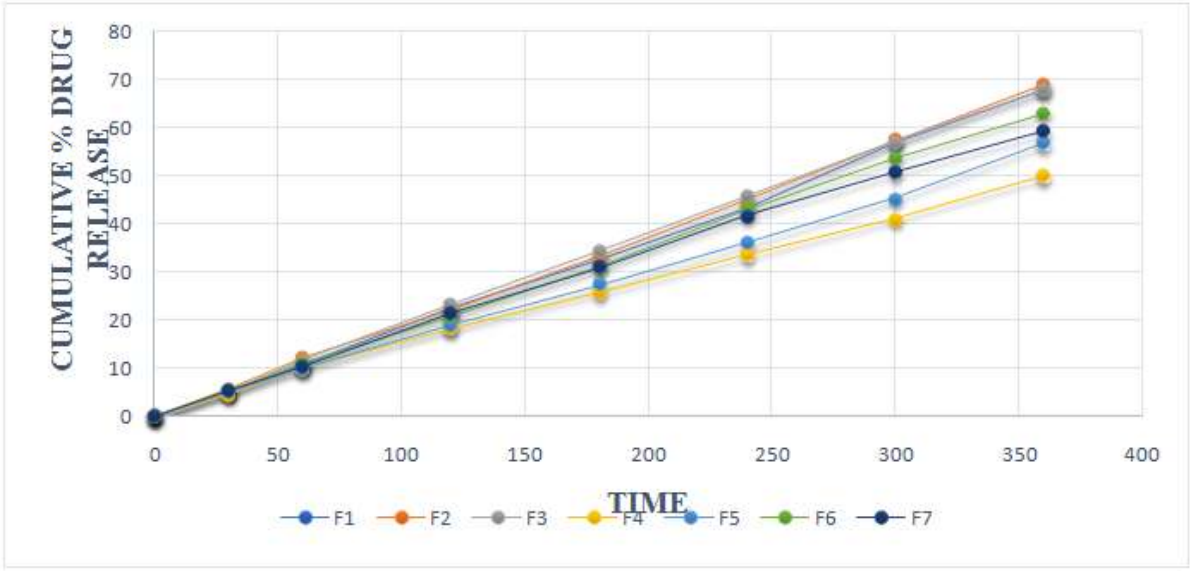

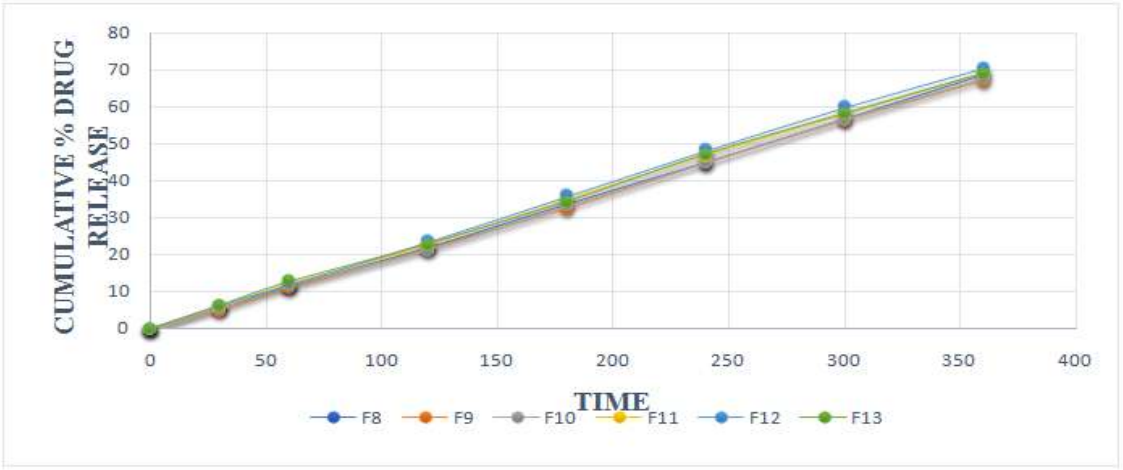

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FIG. 26, 27: % DRUG RELEASE OF INSITU-EMULGEL(F1-F13)

TABLE 55: % DRUG RELEASE OF OPTIMIZED FORMULATION VS PLAIN GEL

S.NO	Time	CUMULATIVE % DRUG RELEASE	
		ISITU-EMULGEL	PLAIN GEL
1.	30	5.29±0.001	4.12±0.002
2.	60	10.39±0.004	8.69±0.001
3.	120	21.46±0.002	18.56±0.005
4.	180	30.79±0.001	26.64±0.002
5.	240	41.54±0.003	34.82±0.004
6.	300	50.61±0.005	43.69±0.003
7.	360	59.02±0.002	51.04±0.005

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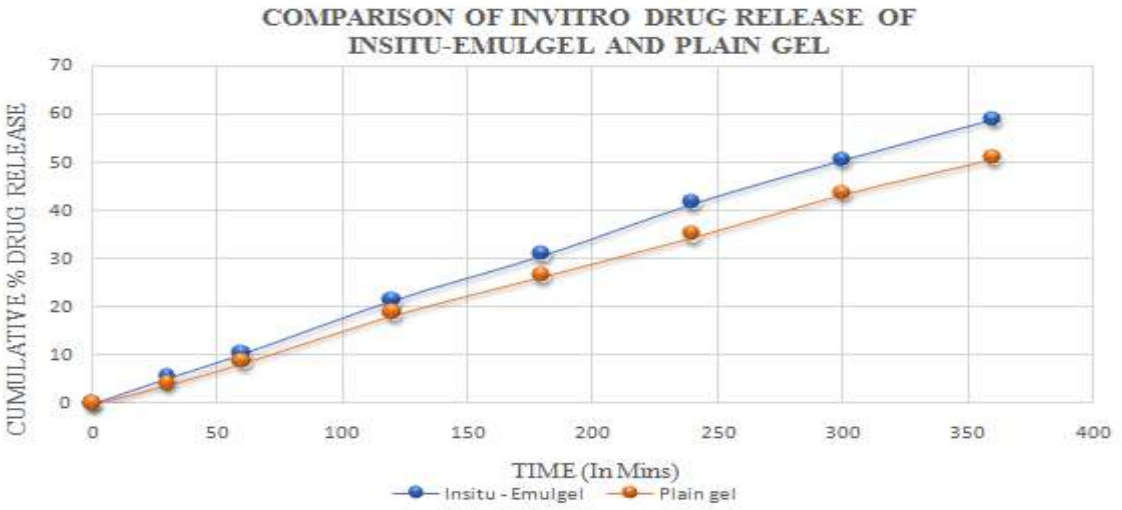

FIG. 28: INVITRO DRUG RELEASE

INFERENCE:

In vitro Release profile of optimized formulation showed 59.02 ± 0.002% release upto 6 hrs. and plain gel showed 51.04±0.005% release upto 6 hrs. This confirms that the drug released form the optimized Insitu-emulgel in a controlled manner.

VI. IN VITRO DRUG RELEASE KINETIC STUDIES:

To analyze the mechanism of drug release-rate kinetics, the results of in-vitro release data canbe plotted in various kinetic models such as zero order, first order, Higuchi and Korsmeyerpeppas model.

S. No	Data fitted in	X-axis	Y-axis	Slope	Intercept	R^2	Linearequation
1	Zero orderreleasekinetics	Time	Cumulative % drugrelease	0.1658	0.6615	0.9986	y = 0.1658x +0.6615
2	First orderkinetics	Time	Logcumulative % drugremaining	-0.0011	2.0139	0.9927	y =-0.0011x +2.0139
3	Higuchi releasekinetics	Cumulative % drug release	Square root time	9.494	0.3005	0.9976	y = 9.494x + 0.3005
4	KorsmeyerPeppaskinetics	Log time	Logcumulative % drugrelease	24.821	4.9514	0.923	y = 24.821x + 4.9514
5	HixsonCrowellkinetics	Time	Cube root ofcumulative % drugremaining	-0.0033	4.6673	0.9978	y = -0.0033x + 4.6673

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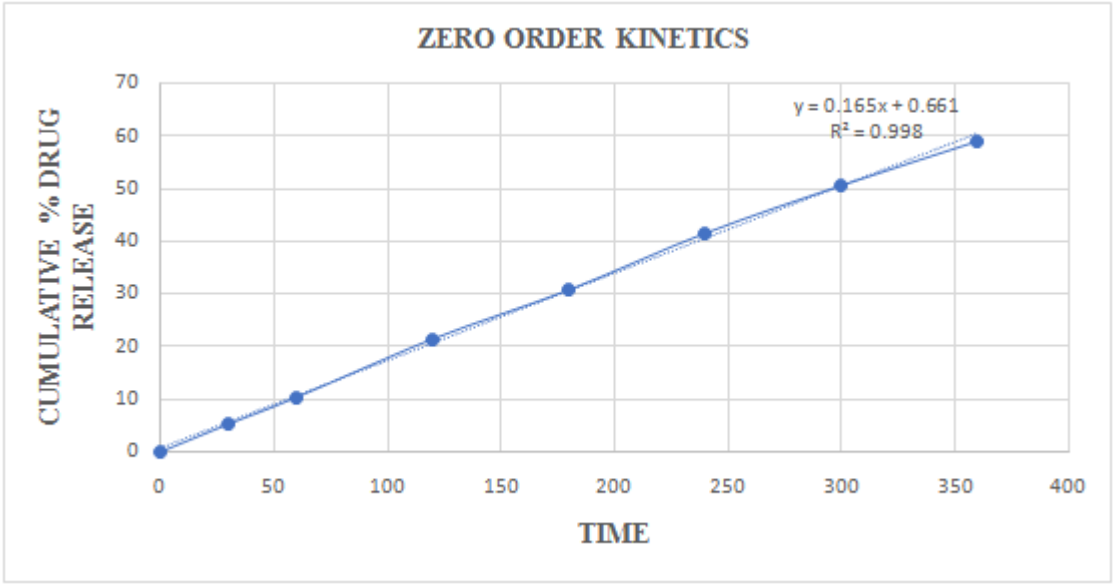

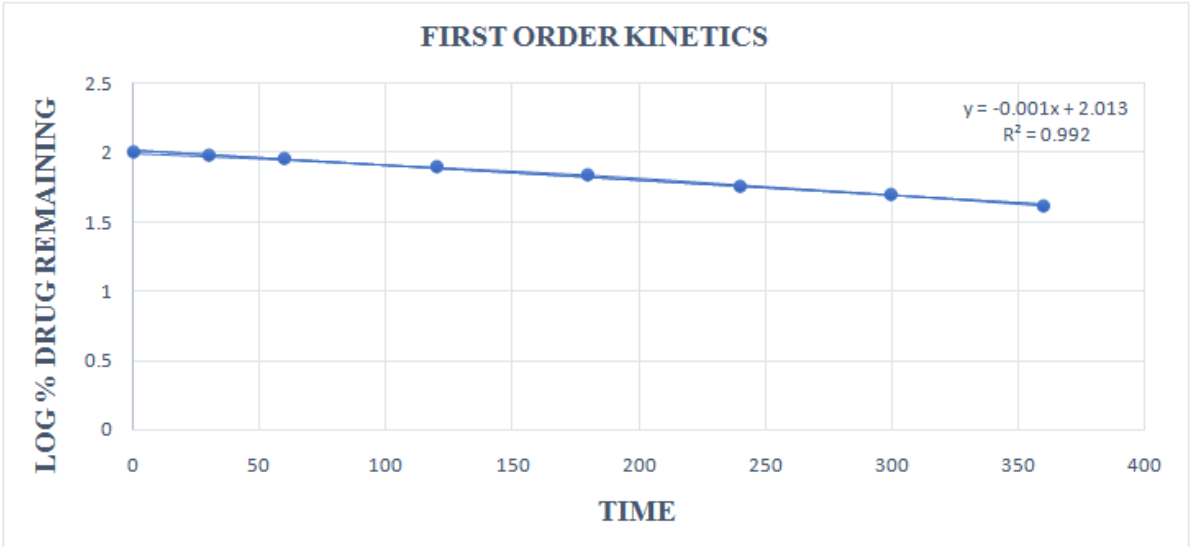

Inference:

Based on the findings, it was determined that the Zero order release kinetics model had the highest correlation coefficient, R^2(0.9986),and was therefore the model that best fit the optimized dutasteride loaded Insitu-emulgel. The fact that the value of "n" was calculated to be 0.1658 (0.45 < n < 0.89), shows that the drug release from the polymeric matrix follows non-Fickian or anomaloustransport. Diffusion and other processes, such matrix swelling, erosion, or relaxation, are all part of there lease mechanism.

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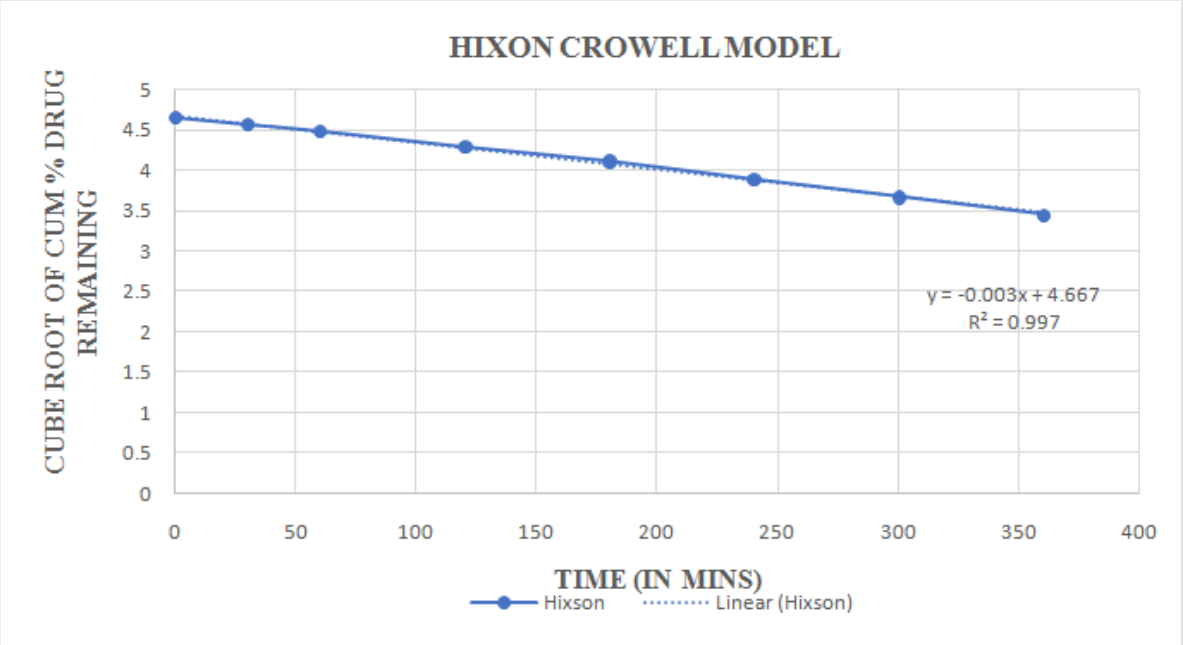

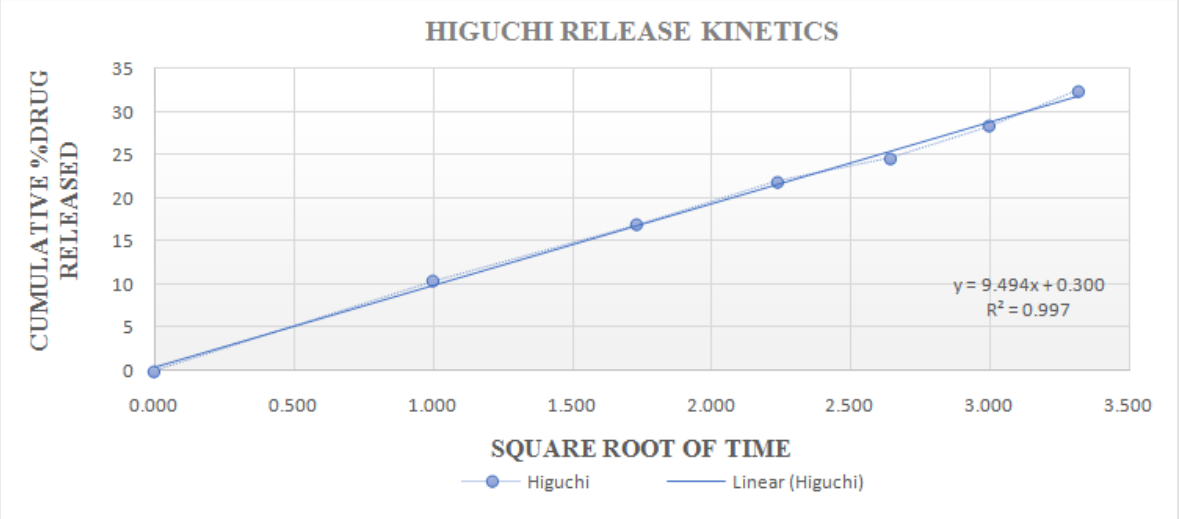

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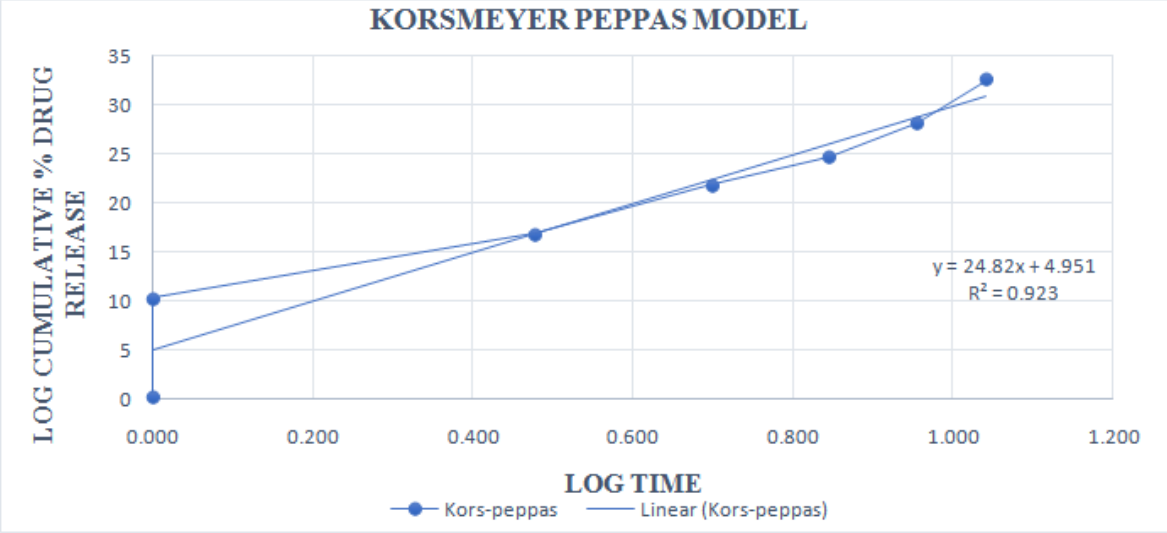

IV. CONCLUSION:

A dutasteride loaded Insitu-emulgel was developed for topical use. When compared to other traditional methods of administering topical medications, Insitu-emulgel seems to be a more sophisticated and efficient drug delivery technology. A large number of the formulations' components are extremely safe and stable for topical use. In order to treat androgenetic alopecia, the present study has succeeded in creating a topical Insitu-emulgel that is safe, economical, and efficient. To increase the effectiveness of treatment and patient compliance, more clinical research is being conducted in this area.

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