RESEARCH ARTICLE

Dutasteride Topical Gel Containing Herbal Extract for Male Pattern Baldness

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ABSTRACT
Topical preparations are utilized to deliver drugs directly to the site of application, ensuring localized effects by penetrating into underlying layers of the skin or mucous membrane, thereby offering primary advantage of avoidance of first-pass metabolism. Dutasteride is mainly used for treating benign prostatic hyperplasia (BPH). The research aimed to develop a topical preparation using dutasteride for treating androgenic alopecia (male pattern baldness) wherein incorporation of onion or garlic extract was explored due to their known benefits in promoting hair growth. Various concentrations of gelling agents were preliminary screened for gel consistency. Here, Carbopol-934 was used as gelling agent, for ease of application and aloe vera as an emollient, which gives lustre to hair. The formulations were evaluated for physico-chemical properties, in-vitro diffusion studies, ex-vivo permeation studies and stability giving desirable results. The preparations were highly productive towards nourishing hair roots and producing faster hair growth. A comparative study of the evaluation parameters for different dutasteride gels formulation demonstrated that the garlic-induced preparation (i.e., dutasteride gel with 10% garlic extract) produced more beneficial effect compared to other preparations, thus this prepared formulation can be suggested for male pattern baldness treatment.

Keywords: Dutasteride, Androgenic Alopecia, Prostatic hyperplasia, Garlic extract, Onion extract.
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INTRODUCTION

Male pattern baldness, also known as androgenic alopecia (AGA), is a genetic disorder that significantly impairs a person's mental health[1,2]. AGA is the most prevalent type of progressive hair loss due to elevated levels of dihydrotestosterone (DHT), a hormone derived from testosterone. DHT targets hair follicles, resulting in miniaturization and eventual hair growth cessation. This procedure emphasizes how crucial it is to address DHT production or its consequences when treating male pattern baldness. The primary androgen in circulation is testosterone; however, in order for testosterone to fully function within the scalp's hair follicles, it must first be converted to DHT, the primary pathogenic androgen of AGA, by the enzyme 5-alpha reductase (5AR)[3]. Dutasteride is primarily used for treating benign prostatic hyperplasia (BPH) and off-label utilized for hair growth due to its unique mechanism of action as a dual 5α-reductase inhibitor. (Figure 1) It is currently being utilized to treat AGA.[4] Dutasteride has shown to be effective in numerous studies[5] and is used off-label in treating patients with AGA throughout the world.[6-8] Dutasteride 0.01% (Worldwide, Australia) injections were given once every 3 months for a total of 3 sessions over the course of six months the results showed enhanced hair growth with improved hair density and diameter. According to another study, weekly low-dose dutasteride and daily finasteride produced outstanding results. Hair follicle size is decreased and the anagen phase is shortened in androgenic alopecia. Thus, creation of novel formulations to halt hair loss and encourage hair growth is crucial.[9] Today, transparent gels utilization has significantly expanded in cosmetics and pharmaceutical preparations. Topical gels serve as ideal delivery system for drugs due to their non-greasy nature and ease of removal from the skin ensuring enhanced patient compliance. A successful and targeted treatment for local action is the delivery of medication to the skin as it eliminates oral administration's first pass effect, GI discomfort and metabolic degradation, this method of drug delivery has grown in popularity.[10] Gels have been suggested as a topical treatment to overcome these drawbacks.[11] Topical preparations' ability to deliver drugs depends on the physicochemical characteristics of both the drug and the vehicle used. To improve skin permeability and medication release, strategies like choosing the right vehicle and co-administering a chemical enhancer[12] are being researched. Gel base composition facilitates medication molecules easy removal from the system compared to cream and ointment.[13,14]. Gels for dermatological use have several beneficial qualities. [15] Onion (Allium cepa) and garlic (Allium sativum) are herbal spices, containing Sulphur compounds including allicin, that promotes hair growth. Research shows that herbal extracts such as onion juice and garlic juice strengthen hair follicles, prevent hair loss and are sure-shot method for

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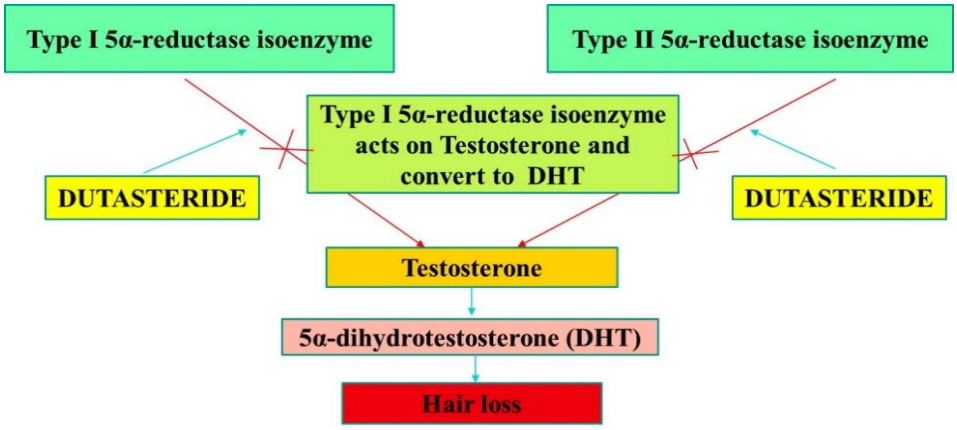

Figure 1: Mechanism of action of Dutasteride.

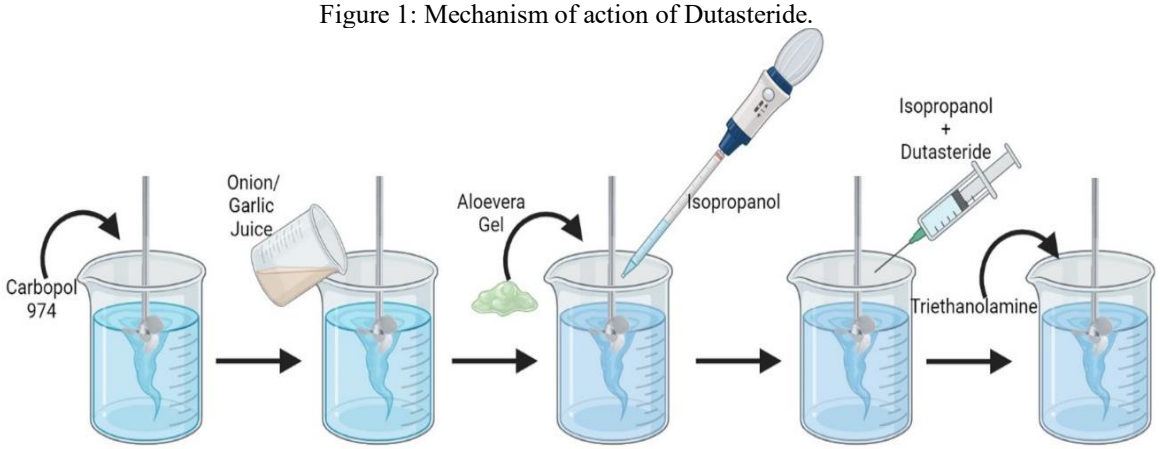

Figure 2: Preparation of gel.

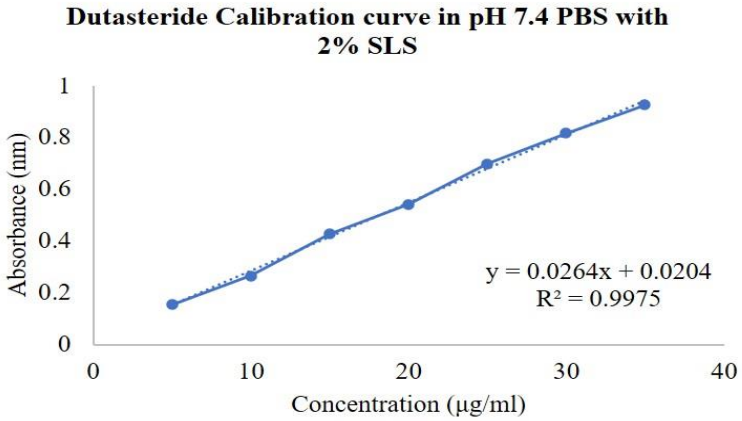

Figure 3: Dutasteride standard graph in pH 7.4 PBS with 2% SLS.

boosting hair growth/regrowth. Thus, in the present study dutasteride gel are prepared by incorporating herbal extracts (onion and garlic) and conducting comparative evaluations of the prepared gels for male pattern baldness.

MATERIALS AND METHODS

Materials

Dutasteride was procured from MSN labs Pvt. Ltd., fresh Onion, Garlic and Aloe vera extract from in house preparation, Triethanolamine from Sisco research laboratories Pvt. Ltd., Isopropanol, Carbopol 974, Sodium lauryl sulphate, Sodium chloride, Disodium hydrogen phosphate, Potassium bromide, Methanol, Sodium nitroprusside, Lead acetate and Sodium hydroxide from S.D. Fine chemicals, Potassium dihydrogen phosphate from Molychem.

Experimental Methodology

Calibration curve for Dutasteride

Dutasteride calibration curve in pH 7.4 PBS (Phosphate Buffer Saline) with 2% SLS was plotted. 5-35µg/ml standard solutions were prepared and absorbance determined using UV-Visible spectrophotometer against blank at λ_{max} of 240nm. Triplicate study was carried and standard graph showing the absorbance *vs.* concentrations

Table 1: Formulation of gels.

Ingredient	*Dutasteride (gm)*	*Carbopol 974 (gm)*	*Garlic Extract (ml)*	*Onion Extract (ml)*	*Aloe vera (ml)*	*Isopropanol (ml)*	*Triethanolamine (ml)*	*Water upto (ml)*
DGX	0.05	0.2	-	-	0.7	3	q.s.	10
DGG1	0.05	0.2	0.1	-	0.7	3	q.s.	10
DGG2	0.05	0.2	0.3	-	0.7	3	q.s.	10
DGG3	0.05	0.2	0.5	-	0.7	3	q.s.	10
DGG4	0.05	0.2	0.7	-	0.7	3	q.s.	10
DGG5	0.05	0.2	1	-	0.7	3	q.s.	10
DGO1	0.05	0.2	-	0.1	0.7	3	q.s.	10
DGO2	0.05	0.2	-	0.3	0.7	3	q.s.	10
DGO3	0.05	0.2	-	0.5	0.7	3	q.s.	10
DGO4	0.05	0.2	-	0.7	0.7	3	q.s.	10
DGO5	0.05	0.2	-	1	0.7	3	q.s.	10

Table 2. Physical evaluation of gels.

Formulation Code	*Clarity*	*Homogenecity*	*PH*	*Spreadability (g.cm/sec)*	*Extrudability*	*Drug Content (%)*	*Viscosity (cps)*
DGX	+++	+++	6.12±0.11	3.75±0.6	+++	86.22±0.27	32600±140
DGG1	+++	+++	6.07±0.11	3.56 ±0.6	+++	71.53±0.23	33400±120
DGG2	+++	+++	6.75±0.12	2.16±0.8	+++	75.73±0.63	37200±130
DGG3	+++	+++	5.70±0.03	4.50±0.3	+++	81.10±0.69	39600±130
DGG4	+++	+++	5.67 ±0.07	2.83±0.7	+++	61.02± 0.80	34200±150
DGG5	+++	+++	5.49 ±0.10	4.33±0.9	+++	88.27±0.18	34600±120
DGO1	+++	+++	6.30±0.11	3.93±0.6	+++	86.20± 0.68	33300±170
DGO2	+++	+++	6.07±0.13	4.84±0.8	+++	85.73±0.60	37200±160
DGO3	+++	+++	5.90±0.03	3.10±0.4	+++	88.02±0.10	38700±110
DGO4	+++	+++	5.85 ±0.07	3.62±0.7	+++	91.57± 0.17	34200±170
DGO5	+++	+++	5.65±0.03	3.56±0.8	+++	93.56±0.38	34500±170

Table 3: Skin deposition and permeation studies for PD, DGX, DGG5 & DGO5.

Formulation Code	*Flux ($\mu g/cm^2/hr$)*	*Permeability coefficient ($cm/hr \times 10^{-3}$)*	*Lag time (hr)*	*Enhancement ratio*	*Skin deposition ($\mu g/cm^2$)*
PD	0.94 ± 0.05	0.82 ± 0.04	0.24 ± 0.64	-	0.67 ± 0.12
DGX	1.83 ± 0.07	1.26 ± 0.09	0.34 ± 0.52	1.94 ± 0.25	0.53 ± 0.24
DGO5	1.67 ± 0.04	0.88 ± 0.02	0.46 ± 0.45	1.77 ± 0.36	0.68 ± 0.36
DGG5	1.95 ± 0.1	1.32 ± 0.06	0.64 ± 0.67	2.07 ± 0.6	0.46 ± 0.16

was plotted from the mean values using which correlation coefficient (r^2) was calculated.

Drug excipients compatibility studies

Spectrum analysis of dutasteride and the polymers utilized to make gels was investigated using FTIR. Shimadzu Corporation (Kyoto, Japan) facility was used to prepare Potassium Bromide (KBr) discs, which were then used to generate FTIR spectra (model - 8400S). This was compared to determine whether any spectral alterations exist in the final spectrum. Also, it was examined for presence of peaks that were typical to the compound's functional group.[16]

Selection of Excipients

Tests for Sulphur content in garlic and onion extract

Fresh garlic/onion were cut into small pieces, smashed using mortar and pestle and the extract or juice was filtered utilizing fresh cheese cloth to remove any foreign matter and contaminants; further the following tests were conducted-

Lead acetate test

2ml of 20% NaOH were added to 2ml of test solution and heated for a minute. A drop of lead acetate solution was added and allowed to cool. The development of a black sulphide precipitate indicates the presence of Sulphur.[17]

Sodium nitroprusside test

Addition of few drops of sodium nitroprusside resulted in purple coloured complex formation indicating presence of Sulphur.[17]

Carbopol

Carbopol gel was prepared in 0.5-2.5% concentrations and the one exhibiting good gelling property along with other excipients was selected to prepare gel.

Preparation of gel

Various herbal hair gel formulations were prepared utilizing Carbopol gel base employing simple gel production technique. Carbopol was dissolved in water and stirred with three-blade stirrer, to this garlic/onion juice, *aloe vera* gel was incorporated and thoroughly mixed. To the clear solution isopropanol was added followed by dropwise addition of dutasteride solution added to another portion of

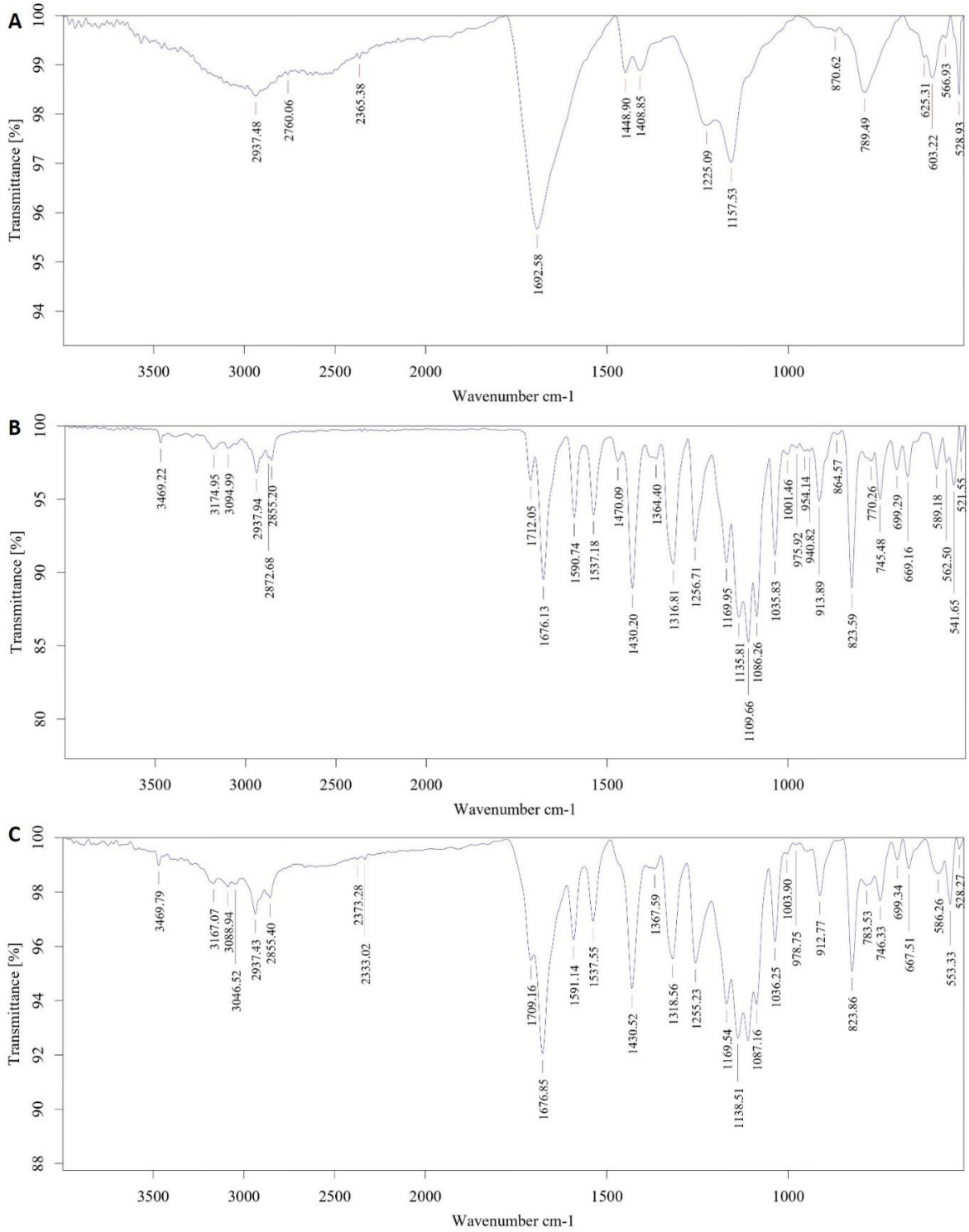

Figure 4: FTIR spectra of (A) Dutasteride, (B) Carbopol- 974 and (C) Drug + Carbopol- 974

isopropanol. Finally, triethanolamine is added dropwise to obtain gel consistency. (Figure 2)

Different types of gels were made in the same manner (DGX- Dutasteride gel, DGG- Dutasteride gel with 1-10% Garlic extract, DGO- Dutasteride gel with 1-10% Onion extract). Table 1 depicts the formulation contents.

Evaluation of topical gels

Gels physiochemical parameters were examined, alongside in-vitro studies and based on the results acquired ex-vivo studies for 10% garlic (DGG5) and 10% onion (DGO5) extract containing dutasteride gels were conducted and compared with pure drug (PD) and plain dutasteride gel (DGX).

Clarity

Clarity was assessed by visual inspection against black and white background graded as:

turbid +, clear ++, very clear +++

Determination of pH

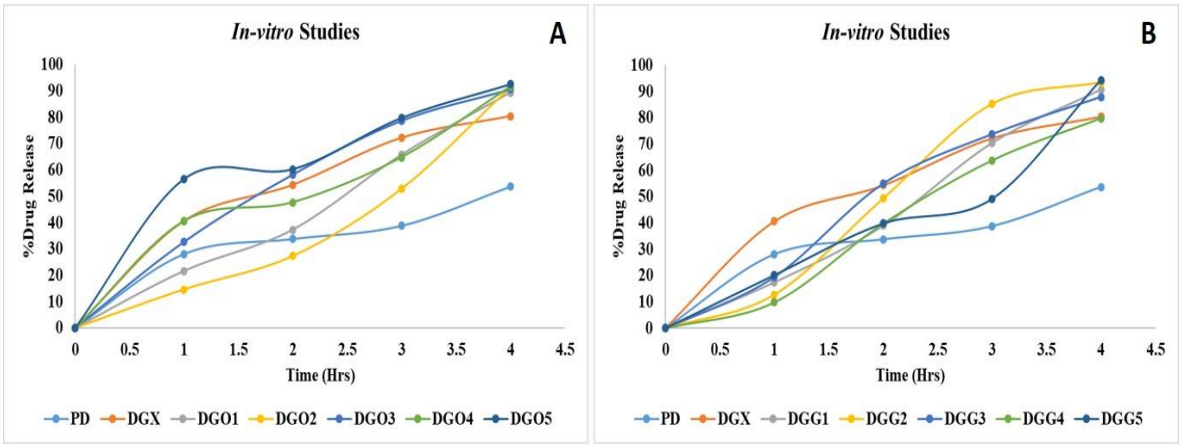

Figure 5. In-vitro studies for (A) Formulations containing onion extract (DGO1-DGO5) and (B) Formulations containing garlic extract (DGG1-DGG5)

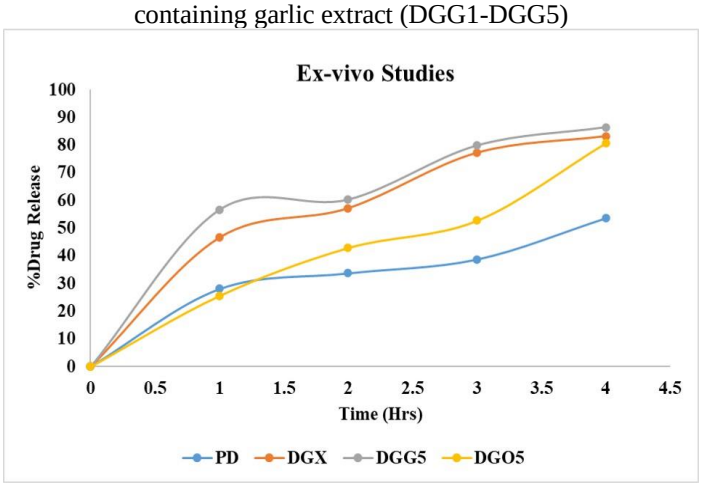

Figure 6: Ex-vivo drug release studies for PD, DGX, DGG5 & DGO5.

Digital pH meter was utilized to determine pH by dispersing 1 g gel in 100ml PH 7.4 PBS with 2% SLS followed by storing for 2 hrs at constant temperature.

Drug content

100mg gel was dissolved in 100ml pH 7.4 PBS with 2% SLS. The volumetric flask was subjected to shaking for 15min followed by passing through Whatman filter paper and after necessary dilutions it was measured at 240nm against corresponding placebo gel.

Homogeneity

Homogeneity for gel appearance and presence of any aggregates [18,19] was assessed by visual inspection & graded as:

Satisfactory +, Good ++, Excellent +++

Extrudability

Pfizer hardness tester was utilised for extrudability testing. 15g capacity aluminium tube was filled with gel and plunger adjusted to hold tube properly. Then 1kg/cm² pressure was applied for 30sec and extruded gel was weighed. At 3 equidistance places of tube the procedure was repeated and % Gel excluded is calculated and graded: 70% as +, 80% as ++ and 90% as +++. [20]

Spreadability

Spreadability was determined by glass plates, measuring spreading diameter of 1g of gel between 20x20cm glass plates after 1 min. the mass of the upper plate was standardized at 150g.

$$S = m * l/t$$

Where, S = spreadability, m = weight tied to the upper glass slide, l = length of the glass slide, t = time taken in seconds.[19, 21, 22]

Determination of viscosity

Utilizing Brookfield viscometer LV DV-II PRO viscosity was determined.[23]

***In-vitro* studies**

Diffusion studies were done utilising Franz diffusion cell fabricated locally, and a 25 ml receptor volume was maintained in receptor compartment. The dialysis membrane was positioned appropriately. Uniformly 100 mg gel formulation was spread on membrane and clamped together. Receptor compartment contained pH 7.4 PBS with 2% SLS, and the hydrodynamics were maintained at a stable 200 rpm using magnetic stirrer.[24] At predetermined intervals, samples (1ml) were collected and replaced appropriately then analysed using an UV-VIS double beam spectrophotometer operating at 240 nm.

***Ex-vivo* permeation studies**

Experimental protocol was approved by IAEC (institutional animal ethical committee). For permeation studies, 25ml receptor volume Franz diffusion cells were utilised with thawed rat skin attached to diffusion cell to keep the dermis side in constant contact with receptor solution. 100 mg gel was applied to stratum corneum facing donor compartment, and hydrodynamics of receptor compartment was kept

Table 4: Model dependent kinetics

Formulation Code	*R^2*				*N*	*Drug transport*
	Zero	*First*	*Higuchi*	*Korsmeyer peppas*		
PD	0.9259	0.9659	0.8752	0.8808	0.4268	Fickian diffusion
DGX	0.9627	0.9570	0.9633	0.9613	0.4388	Fickian diffusion
DGG5	0.932	0.9318	0.9053	0.8692	0.3213	Fickian diffusion
DGO5	0.9617	0.9763	0.9308	0.9694	0.7819	Anomalous Transport

Table 5: Stability Studies for DGG5.

Evaluation parameters	*Period of stability studies*				
	Day 0	*Day 7*	*Day 14*	*Day 21*	*1 month*
Physical appearance	Clear gel	Clear gel	Clear gel	Clear gel	Clear gel
Drug content (%)	88.27±0.18	88.15±0.35	88.12±0.25	88.06±0.15	88.01±0.05
Ex-vivo permeation (%)	86.40±0.46	86.36±0.01	86.23±0.04	86.18±0.06	86.05±0.07

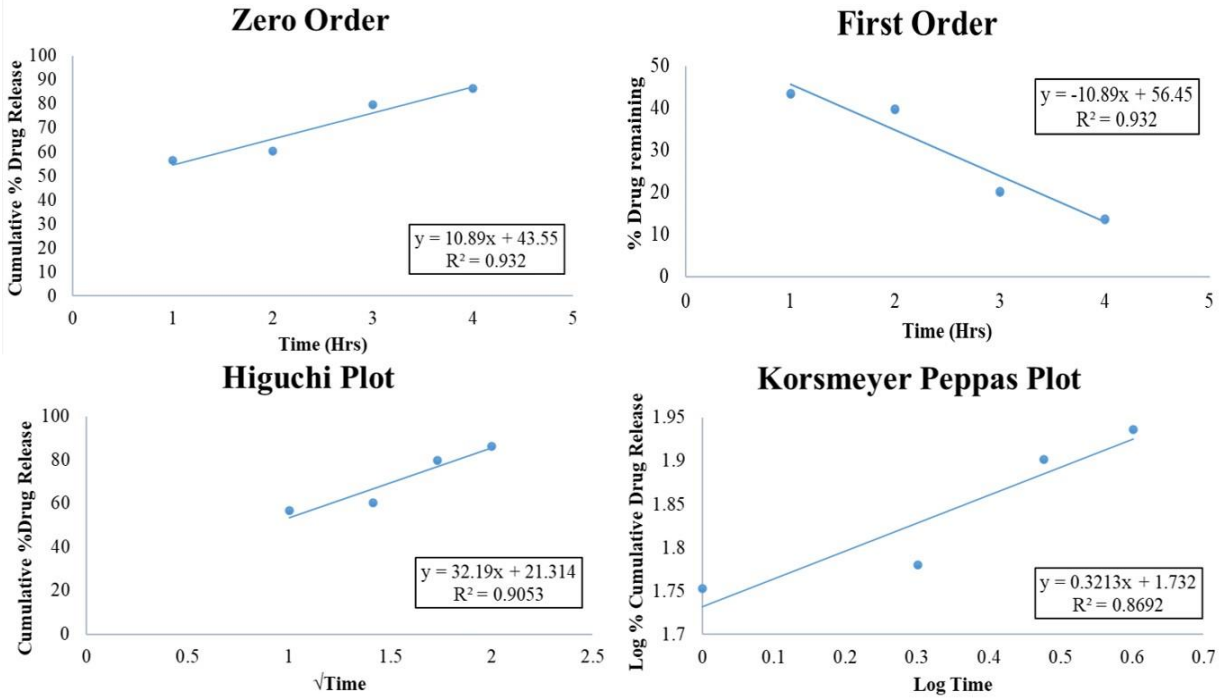

Figure 7: Model-dependent kinetics for DGG5

stable throughout. Over a period of 3hrs, 1ml samples were collected and drug content measured. For the percutaneous absorption of dutasteride, ex-vivo permeation, percent drug release, cumulative amount penetrated per square centimeter in 3 hours (Q3), flux, permeability coefficient, lag time and enhancement ratio were computed[25, 26] according to Singh et al. [27]

Model dependent kinetics

Release data acquired for PD, DGX, DGG5 and DGO5 were fitted into different kinetic models to determine release kinetics and release mechanism.

Stability Studies

Based on evaluation results, optimized dutasteride gel with 10% garlic extract (DGG5) was stored as per ICH guidelines at accelerated stability conditions (40°C ± 2°C/75% ± 5% RH) for 1 month and evaluated for physical appearance, ex-vivo permeation and drug content every week.

RESULTS AND DISCUSSION

Construction of Dutasteride calibration curve

An absorption maximum (λ_{max}) of 240nm was obtained. Standard curve was obtained by plotting absorbance against concentration on X-axis. (Figure 3) The R^2 value of 0.997 shows the linearity for 5-35µg/ml concentrations.

Drug-excipient compatibility studies

The absence of any significant changes or shifts in the spectra of optimized formulation confirms no interaction between excipients and drug. Also, absence of any alteration in pure drug functionally indicates compatibility with formulation excipients. (Figure 4)

Selection of Excipients

Testing garlic and onion extract for Sulphur content

Lead acetate test

The development of the black sulphide precipitate, indicated presence of Sulphur in the herbal extracts.

Sodium nitroprusside test

The appearance of purple coloration in test sample indicated presence of Sulphur in the herbal extracts.

Carbopol

Out of 0.5 to 2.5% concentrations Carbopol gels prepared 1% and 1.5% were found to exhibit good gelling property but due to other excipients gel viscosity was affected. So, 2% Carbopol was selected to prepare gel.

Evaluation of transdermal gels

Physiochemical parameters

The prepared gel was evaluated and was found to be clear, homogenous with good spreadability and extrudability; having pH 5.49 ± 0.10 - 6.75 ± 0.12, drug content 61.02 ± 0.80 - 93.56 ± 0.38 %, spreadability 2.16 ± 0.8 - 4.84 ± 0.8 g.cm/sec and viscosity 32600 ± 140 - 39600 ± 130 cps, all of which are within the ideal desirable range (Table 2)

***In-vitro* studies**

This was performed utilizing dialysis membrane for the prepared gel formulations and the % Drug release for the formulated gels containing onion extract was in the range of 89.4 ± 0.75 - 92.6 ± 0.23 %, for gels containing garlic extract was 79.7 ± 0.34 - 94.2 ± 0.46 % while for plain dutasteride gel was 80.4 ± 0.67 % and pure drug 53.13 ± 0.78 %. (Figure 5)

***Ex-vivo* permeation studies**

Permeability studies were performed and permeability parameters were calculated for PD, gel formulations- DGX, DGO5 & DGG5 which are displayed in Table 3. The ex-vivo drug release for these was 53.63 ± 0.32%, 83.2 ± 0.42%, 80.7 ± 0.25% and 86.4 ± 0.75%, respectively at 4hrs. (Figure 6)

Among the formulations DGG5 containing garlic 10% showed enhancement of 2.07 ± 0.6 when compared with pure drug. Formulation DGO5 containing onion 10% showed similar release of drug as plain dutasteride gel DGX. So DGG5 formulation was optimized.

Model dependent kinetics

The release data acquired for PD, DGX, DGG5 and DGO5 was fitted into different kinetic model. Table 4 depicts release kinetics and mechanism for each formulation. DGG5 shows first-order kinetics with release mechanism by fickian diffusion. (Figure 7)

Stability Studies

Stability studies were performed for 10% Garlic extract containing gel (DGG5) and the data revealed no significant changes indicating the prepared formulation to be stable for one month. (Table 5)

CONCLUSION

Male pattern baldness nowadays can be seen in many people irrespective of region, race and genetics due to many factors like lifestyle, pollution, improper diet, stress etc., and this will be a prime problem in future youngsters and general population. Dutasteride gels along with fresh onion and garlic extract were prepared and evaluated for various parameters wherein evaluation results were found to be in acceptable range. Better results were obtained for dutasteride gel comprising 10% Garlic extract i.e., DGG5 formulation compared to pure drug (PD), gel formulations with alone dutasteride (DGX) and with combination of onion extract (DGO). Hence, it is concluded that prepared dutasteride topical gel comprising garlic extract acts as an adjuvant and helps in more hair growth. The formulation comprising herbal ingredient assures lower side effects when compared to other synthetic hair growth preparations. Also, it is highly productive towards nourishing hair roots and producing faster hair growth, thus this can be recommended for treating male pattern baldness.

Future Scope

Further animal studies need to be performed to check hair growth and for the optimized gel formulation (DGG5) pharmacokinetics parameter must be determined.

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