Development of Suppositories Containing Flutamide-Loaded Alginate-Tamarind Microparticles for Rectal Administration: In Vitro and in Vivo Studies

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In the present work the absorption of flutamide from suppositories containing hydrophilic tamarind alginate microparticles after rectal administration in rats was investigated with the purpose of enhancing bioavailability and to avoid hepatic toxicity. Microparticles were developed by ionic gelation method and optimized using one factorial design of response surface methodology. The optimized batch of microparticles had tamarind gum–sodium alginate (1:3) ratio and showed entrapment efficiency 94.969% and mucoadhesion strength 94.646% with desirability of 0.961. Suppositories loaded with microparticles were developed by fusion method using poloxamer 407 and poloxamer 188 in combination as suppository base. Kinetic analysis of the release data of microparticle-loaded suppositories showed time-independent release of drug. Higher values of $n^*$ ($>0.89$) represent Super Case II-type drug release. The pharmacokinetics of flutamide from flutamide tamarind alginate microparticle-loaded suppository were compared with oral suspension. $C_{\text{max}}$ of microparticle-loaded suppository was significantly larger than that of oral suspension (1.711 and 0.859 µg/mL, respectively).

Key words tamarind kernel polysaccharide; sodium alginate; ionic gelation; one factorial design; mucoadhesive microparticle-loaded poloxamer suppository; rectal delivery

Adenocarcinoma of the prostate is the second most common cause of death of men world-wide. A nonsteroidal antiandrogen flutamide could be used in combination with medical or surgical castration to provide superior care for patients with metastatic prostate cancer. Large studies have shown a longer disease-free interval and a short survival advantage with maximum androgen blockade compared with monotherapy; especially in younger, healthy patients with minimum metastatic disease.1)

Flutamide is a potent nonsteroidal antiandrogen drug that inhibits androgen uptake and/or nuclear binding of androgen in target tissues. It is chemically known as 2-methyl-N-[4-nitro-3-(trifluoromethyl)phenyl]propanamide. Flutamide competes with testosterone and its powerful metabolite, dihydrotestosterone for binding to androgen receptors in the prostate gland.2)

The low oral bioavailability of flutamide may be due to poor wettability, low aqueous solubility, poor permeability, extensive first pass metabolism and low availability at absorption site. Several attempts have been made to improve oral bioavailability and to reduce side effects of flutamide such as nanoemulsions,3) hydroxypropyl-β-cyclodextrin (HP-βCD) inclusion complex,4) nanoparticles,5) lyophilised dispersions with βCD and HP-βCD,6) hydrophilic polymers,7) polyols and amino acids,8) biopolymeric microparticles combined with lyophilized monophase dispersions.9) However, rectal administration of flutamide in the interest of bioavailability enhancement has never been discussed or examined.

The advantage of rectal route over oral route of administration is avoidance of first pass metabolism and gastrointestinal side effects. For effective retention of medication on the rectal mucosa, the drug delivery system should have mucoadhesive property.

Microparticulate drug delivery system is one of the prospective drug delivery systems because it has advantages, such as effective and long lasting release of drug, protection of drug from inactivation, capacity to reduce drug toxicity, reduced number of doses required for treatment of the diseases, and smaller dose variations due to administration of large number of microparticulates. Mucoadhesive polymers make the microparticles able to promote intimate contact between the pharmaceutical form and targeted tissue and to prolong the residence time of drug at the site of administration.

Natural polymers are widely used as drug carriers as these have advantages like low cost, biocompatibility, and biodegradability.10) Alginate is an anionic copolymer of 1,4-linked β-d-mannuronic acid and α-L-guluronic acid, can be used for encapsulation of a wide range of drugs, with minimal use of organic solvents.

Tamarind kernel powder, derived from the seeds of Tamarindus indica. A common and most important tree of India and Southeast Asia belongs to the family Leguminosae. Tamarind kernel powder is composed of xyloglucan polysaccharide which is (1,4)-linked β-D-glucan backbone chain, which has (1,6)-linked α-L-xyllose branches that are partially substituted by (1,2)-linked β-D-galactoxylose. For use in drug-release studies polymer is partially degraded by β-galactosidase to eliminate 44% of the galactose residues.11)

Tamarind gels are non-toxic, cause no detectable damage to rectal mucosa and can be effectively used in rectal administration of drugs, are subject to extensive first pass metabolism.12) Chloromazole-loaded polaxamer-propylene glycol based suppository which was effective rectal dosage form for the treatment of tumours and found to decrease the hepatotoxic-
ity compared to oral administration in rat. Microcapsules of theophylline and oxynphenbutazone were prepared with different ratios of polyethylene to ethyl cellulose and incorporated in polyethylene glycol suppositories. Mucoadhesive microspheres based on gelatin and its admixtures with porcine mucin were enhanced the rectal availability of cefuroxime microspheres based on gelatin and its admixtures with porcine mucin were enhanced the rectal availability of cefuroxime microspheres. Ketoprofen sodium through entrapment into the microspheres and also mucin were enhanced the rectal availability of cefuroxime microspheres. 14) Mucoadhesive of theophylline and oxyphenbutazone were prepared with different ratios of polyethylene to ethyl cellulose and incorporated in polyethylene glycol suppositories.

Extended survey of literature and patent databases did not reveal any microparticles loaded suppository formulation developed of flutamide. Based on these considerations, the main objectives of the present study were: i) To develop flutamide microparticles by ionic gelation method using natural hydrophilic polymers sodium alginate and tamarind kernel powder in combination. ii) To characterise the microparticles formulation in terms of size, entrapment efficiency, morphology, and physicochemical properties using X-ray diffraction (XRD), differential scanning calorimetry (DSC). iii) To develop suppository of optimised microparticles formulation. iv) To carry out in-vivo study.

**Experimental**

**Materials** Flutamide was obtained as a gift sample from Cipla Ltd. (Mumbai, India). Tamarind kernel powder (TKP) was obtained from Hindustan Gums and Chemicals Pvt. Ltd. (Bhiwani, India).

Sodium alginate and calcium chloride were obtained as gratitude samples from Thomas Baker Chemicals Pvt. Ltd. (Mumbai, India) and Poloxamer 407 (P407) and poloxamer 188 (P188) from Mylan Laboratories (Nasik, India). Freshly excised rectal cavity was obtained from the local butcher shop (Nasik, India). Methanol and acetonitrile used was HPLC grade from Rankem Ltd., India. Water used was HPLC grade from Rankem Ltd., India and was rinsed with normal saline. The mucosa was then pinned onto a polyethylene support inclined at an angle of 60°. A 25 number (No) of counted flutamide-loaded alginate tamarind microparticles formulated with various ratios of the polymers were placed on the trough of the mucosal surface, were allowed to hydrate with water for 15 min. A 50 mL of pH 6.8 phosphate buffer was allowed to flow over the tissue at the rate of 40 drops/min. The number of the microparticles adhering on mucosal surface (Ns) was counted. The adhesive strength was determined using following formula:

\[
\% \text{ Mucoadhesive strength} = \frac{N_s}{N_0} \times 100
\]

**In Vitro** Mucoadhesive Strength of Microparticles Using Falling Liquid Film Technique

Fifty milligram sample of each batch of flutamide-loaded alginate tamarind microparticles was triturated in mortar and shaken vigorously with 50 mL of methanol and left for 12 h for complete drug extraction. This dispersion was then filtered through membrane filter, diluted to desired concentration with water and analyzed spectrophotometrically at 227 nm. %EE was calculated by using following formula.

\[
\% \text{ EE} = \frac{\text{Practical amt. of drug entrapped in microparticles}}{\text{Theoretical amt. of drug added in microparticles}} \times 100
\]

**Production Yield**

Production yields were determined using following formula.

\[
\text{Production yield} = \frac{\text{Practical yield of microparticles after drying}}{\text{Theoretical yield}} \times 100
\]

\[
\text{Total amt of drug and polymers added initially}
\]

**Experimental Design**

The preparation of flutamide-loaded alginate tamarind microparticles was carried out using Design Expert 8.0.7.1 software by one factorial design of response surface methodology. The concentration of sodium alginate was selected as independent variable based on preliminary studies. All other processing variables were kept invariant throughout the study. % Production yield, % entrapment efficiency and % muco-adhesive strength were taken as response variables. In all, 7 experimental runs were carried out as shown in Table 1.

### Table 1. Formulation of Flutamide-Loaded Alginate Tamarind Microparticles Using One Factorial Design of Response Surface Methodology

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Tamarind kernel powder (TKP) (% w/v)</th>
<th>Sodium alginate (% w/v)</th>
<th>Y1 (production yield)</th>
<th>Y2 (% EE)</th>
<th>Y3 (% mucoadhesive strength)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>1</td>
<td>0.5</td>
<td>90.033</td>
<td>92.773</td>
<td>93.333</td>
</tr>
<tr>
<td>T2</td>
<td>1</td>
<td>1.0</td>
<td>93.104</td>
<td>94.969</td>
<td>94.646</td>
</tr>
<tr>
<td>T3</td>
<td>1</td>
<td>0.0</td>
<td>81.195</td>
<td>96.039</td>
<td>90.667</td>
</tr>
<tr>
<td>T4</td>
<td>1</td>
<td>1.0</td>
<td>90.317</td>
<td>95.470</td>
<td>93.333</td>
</tr>
<tr>
<td>T5</td>
<td>1</td>
<td>1.0</td>
<td>85.400</td>
<td>94.646</td>
<td>90.667</td>
</tr>
<tr>
<td>T6</td>
<td>1</td>
<td>−0.5</td>
<td>78.087</td>
<td>82.793</td>
<td>90.667</td>
</tr>
<tr>
<td>T7</td>
<td>1</td>
<td>−1.0</td>
<td>88.683</td>
<td>81.803</td>
<td>85.333</td>
</tr>
</tbody>
</table>

\[\text{Sodium alginate}\quad 1.0=1\%\ w/v;\quad -0.5=1.5\%\ w/v;\quad 0.0=2\%\ w/v;\quad 0.5=2.5\%\ w/v;\quad 1.0=3\%\ w/v.\]
In Vitro Release Study of Flutamide-Loaded Alginate Tamarind Microparticles

Optimized batch of flutamide-loaded alginate tamarind microparticles equivalent to 60 mg of flutamide was weighed accurately and subjected to release rate study in pH 6.8 phosphate buffer using USP dissolution test apparatus II (Model: Tablet Dissolution Test Apparatus, Labindia) with autosampler. Flutamide was used as control and subjected to release rate study by weighing 60 mg of it. Samples were periodically withdrawn and replaced with same volume of fresh buffer solution, and assayed using a spectrophotometer at 227.7 nm.

Particle Size Analysis

Particle size was analyzed by dispersing microparticles in immersion oil. Analysis was carried out using Motic DMW2-223 digital microscope (Motic Instruments Inc. Canada) equipped with a 1/399 CCD camera imaging accessory and computer controlled image analysis software (Motic images 2000, 1.3 version).

Zeta Potential Study

The dispersion of microparticles in distilled water was filled in zeta cell and placed in the Zeta Sizer (Nano ZS90, Malvern Instruments, U.K.).

Scanning Electron Microscopy (SEM)

The surface morphology of the optimized flutamide-loaded alginate tamarind microparticles was studied using a scanning electron microscope (JSM 6390, JEOL) operated at an accelerating voltage of 10 kV.

DSC

The thermal behavior of pure drug, flutamide-loaded alginate tamarind microparticles and blank microparticles were studied using a differential scanning calorimeter (Mettler-Toledo AG Analytical, Switzerland) at a heating rate of 10°C/min. The measurements were performed at a heating range of 40–300°C under nitrogen atmospheres.

XRD

X-Ray diffractogram of pure drug, blank microparticles and flutamide-loaded alginate tamarind microparticles were recorded by Philips-PW-1050 scanner (PANalytical, the Netherlands) with filter Ni, Cu-Kα radiation, voltage 40 kV and a current of 30 mA. All samples were measured in the diffraction angle (2θ) range between 10° to 80° and 0.020° step size.

Formulation of Flutamide-Loaded Alginate Tamarind Microparticles

Optimised batch of flutamide-loaded alginate tamarind microparticles was developed as suppository using different proportion of suppository bases Poloxamer 407–Poloxamer 188 (99:1, 98:2, 97:3). Suppository contains 5% microparticles and 95% suppository base. P407–P188 were mixed in different proportion and heated up to 55°C. Flutamide loaded alginate tamarind microparticles were then slowly added to the solution with continuous agitation. The resulting solution was then placed into the suppository containing required amount of flutamide-loaded alginate tamarind microparticles with different proportions of P407–P188 as 99:1, 98:2, 97:3 was inserted into semi permeable membrane tube. Both sides of the tube were closed by tying a thread to prevent leakage and then subjected to release rate study in pH 6.8 phosphate buffer using USP dissolution test apparatus II (Model: Tablet Dissolution Test Apparatus, Labindia) with autosampler. Sampling volume of 5 mL was withdrawn at predetermined time intervals and replaced by equal volumes of fresh dissolution medium. The drug concentration in the sample was determined from the standard curve of the drug in pH 6.8 phosphate buffer at 227.7 nm.

Kinetic Modelling of Release Data

In order to understand the drug release mechanism from the polymer system, the power law (Peppas equation) is used to analyse the results.

\[
\frac{M_t}{M_\infty} = kt^n
\]

Where \(M_t/M_\infty\) is the fractional release of the drug at time \(t\), \(k\) is the constant related to the structural and geometric characteristics of the device, and \(n\) is the swelling exponent, indicative of the drug release mechanism. The diffusional exponent, \(n\), specifies the mechanism of release. Values of \(n\) between 0.43 and 0.85 are an indication of both diffusion controlled drug release and swelling controlled drug release (anomalous transport). Values above 0.85 indicate case-II transport which relate to polymer relaxation during gel swelling. \(^{22,23}\)

Stability Study

Stability study of optimized formulation of flutamide-loaded alginate tamarind microparticles was carried out for 3 months at 40±2°C/75±5%RH as per ICH guidelines. Microparticles of optimized batch were placed in sealed vials which were then stored at 40°C/75%RH for 90 days in stability chamber. The physical properties, % EE and drug release rate of the optimized batch were determined 1, 2, and 3 months interval.

For short term stability study of suppository, the suppositories were individually wrapped in aluminum foil and packed in cardboard boxes and were kept at refrigeration temperature (4°C) for 6 weeks. Samples are taken after 6 weeks for physical appearance and drug content estimation. \(^{24}\)

In Vivo Study

Male Sprague-Dawley Rats with body weights ranging from 350–400 g were fasted for 36 h before the experiment with free access to water. The animals were classified into 2 groups with 5 animals in each group. The protocol for this investigation was approved by the Institutional Animal ethics committee in accordance with the disciplinary principles and guidelines of CPCSEA (Committee for the purpose of control and supervision of experiments on animals). Oral suspension of flutamide and flutamide tamarind alginate microparticles were loaded suppository with equivalent dose (15 mg/kg) were given separately to each group. After administration of different formulations blood sample (0.5 mL) will be collected through retro-orbital plexus at time intervals of 0, 30 min, 1, 2, 3, 4, 5 and 24 h. \(^{25}\)

The whole blood samples were centrifuged to obtain plasma, which was analysed for flutamide. The plasma was spiked with 0.4 mL of ethyl acetate, centrifuged at 4°C at 10000 rpm. After centrifugation, organic layer was isolated and evaporated under nitrogen. The tubes were reconstituted with respective mobile phases and the samples were used for chromatographic analyses. HPLC conditions were optimised to reduce interferences with other plasma proteins, if any. Chromatographic analyses were carried out using acetoniitrile and 0.05 M KH₂PO₄ pH 4.5 (60:40) as the mobile phase, at 238 nm at flow rate of 1 mL/min. Column used was Kromasil C18, 150×4.6 mm. \(^{25}\)

Results and Discussion

Formulation of Flutamide-Loaded Alginate Tamarind Microparticles

It has been reported that polymers with pos-
The reaction of TKP and sodium alginate, with multivalent cation like calcium chloride (cation crosslinker) allows the formation of bridges between the polymeric chains and results in inter-cross-linking (by electrostatic interaction) between the polymer molecules, which might have eventually resulted in efficient adsorption of polymer (hydrophilic) on drug particles. Hence, in the present work, we prepared different polymeric-based microparticulate systems in order to improve the solubility, dissolution properties and hence absorption of flutamide.

### Optimization Data Analysis and Model-Validation

#### Fitting of Data to the Model
In one factorial design different concentrations of sodium alginate (1, 1.5, 2, 2.5, 3%) were utilized. The ranges of responses $Y_1$, $Y_2$ and $Y_3$ were 78.087–93.1, 81.803–96.04 and 81.33–94.66%, respectively (Table 1). All the responses observed for seven formulations prepared were fitted to various models using Design-Expert software. It was observed that the best fitted models were cubic for both production yield and entrapment efficiency, and linear for mucoadhesion strength. The values of $R^2$, adjusted $R^2$, predicted $R^2$, standard deviation (S.D.) and %CV are given in Table 2 along with the regression equation generated for each response. The results of ANOVA for the dependent variables demonstrate that the model was significant for all response variables.

### Optimization and Validation
A numerical optimization technique with desirability approach was used to select the desired polymer combination under the constraints of maximizing both entrapment efficiency as well as mucoadhesion strength. Formulation with tamarind gum–sodium alginate (1:3) ratio has production yield 93.104%, entrapment efficiency 94.969% and mucoadhesion strength 94.646% with desirability of 0.961 was optimized.

### Particle Size Analysis
Size ranges from 889.58–994.92 µm. Size of extrusion device and the viscosity of polymer solution were mainly affecting the particle size of microparticles prepared by ionic gelation method. Increase in the concentration of polymer, increases the viscosity of polymer solution, formed larger droplets and produce microparticles with large particle size. Decrease in concentration of polymer decreases the viscosity of polymer solution henceforth decreases particle size. Other researchers have reported similar results.26,27 Increasing the size of extrusion device increased the particle size of microparticles. Needle no. 26 was found suitable for the formulation of microparticles.

#### Zeta Potential Study
The zeta potential of flutamide-loaded alginate tamarind microparticles and blank microparticles were −7.76 and −10, respectively. The microparticles prepared were negatively charged, indicating the presence of anionic polymer at the surface of all microparticles. Increase in zeta potential observed from blank to drug loaded microparticles i.e., from −10 to −7.76. Due to interaction between anionic moiety of TKP and alginate with cationic moiety of flutamide or negatively charged groups interact with molecules of opposite charges to form three-dimensional (3-D) networks.

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**Table 2. Summary of Regression Analysis Results for Responses $Y_1$, $Y_2$ and $Y_3$**

<table>
<thead>
<tr>
<th>Models</th>
<th>$R^2$</th>
<th>Adjusted $R^2$</th>
<th>Predicted $R^2$</th>
<th>S.D.</th>
<th>% CV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response $Y_1$ (% production yield)</td>
<td>0.9581</td>
<td>0.9162</td>
<td>0.8276</td>
<td>1.40</td>
<td>1.62</td>
</tr>
<tr>
<td>Cubic model</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\text{Eq}^3: Y_1=80.91+11.72X+7.94X^2-9.88X^3$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Response $Y_2$ (%EE)</td>
<td>0.9750</td>
<td>0.9500</td>
<td>0.7684</td>
<td>1.47</td>
<td>1.64</td>
</tr>
<tr>
<td>Cubic model</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\text{Eq}^3: Y_2=91.13-19.76X-0.444X^2+26.05X^3$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Response $Y_3$ (% mucoadhesion strength)</td>
<td>0.7137</td>
<td>0.6564</td>
<td>0.4634</td>
<td>2.85</td>
<td>3.17</td>
</tr>
<tr>
<td>Linear</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\text{Eq}^1: Y_3=89.90+4.74X$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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![SEM Images of Flutamide Loaded Alginate Tamarind Microparticles](image)
flutamide during microparticle formulation, increase in zeta potential may observed in drug loaded microparticles. Strong anionic charge on the polymer is one of the required characteristics for mucoadhesion.28)

**Surface Morphology** SEM analysis showed irregular shaped microparticles with rough and intact surface (Fig. 1). The rough surface may impart strong adhesion.18)

**XRD**
X-Ray diffractogram of flutamide indicates crystalline nature of drug. In contrast the blank and flutamide-loaded alginate tamarind microparticles, absence of crystalline peaks of drug in blank microparticles whereas presence of some peaks in drug loaded microparticles indicates the evidence of micro-encapsulation of drug with polymer (Fig. 2).

**DSC** The thermogram of flutamide exhibited a sharp endothermic peak at 112.82°C indicated melting point which was reported in the literature. Characteristic sharp peak of flutamide was disappeared in the Flutamide loaded alginate

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![Figure 2](image2.png)

**Fig. 2.** X-Ray Diffractogram of (A) Flutamide (B) Blank Alginate Tamarind Microparticles (C) Flutamide Loaded Alginate Tamarind Microparticles

![Figure 3](image3.png)

**Fig. 3.** DSC Thermogram of Flutamide, Flutamide Loaded Alginate Tamarind Microparticles and Blank Microparticles

![Figure 4](image4.png)

**Fig. 4.** Release Profiles of (A) Flutamide (B) Flutamide-Loaded Tamarind Alginate Microparticles (C) Flutamide Tamarind Alginate Microparticles Loaded Suppository 1 P407/P188 (99/1%); (D) Suppository 2 P407/P188 (98/2%); E) Suppository 3 P407/P188 (97/3%)
tamarind microparticles. DSC studies revealed that flutamide were molecularly dispersed inside of the microparticles (Fig. 3).

**In Vitro Drug Release Study** Drug release from Flutamide loaded alginate tamarind microparticles was due to penetration of water in the matrix, hydration, swelling, diffusion of the dissolved drug (polymer hydro fusion), and/or the erosion of the gelatinous layer. Alginate degraded rapidly due to exchange of Ca$^{2+}$ ions binding to carboxyl groups of alginate and phosphate ions of the medium. Considerable increase in dissolution rate of all suppositories was attributed to surfactant nature of poloxamers. Hydrophilic portions of the poloxamers probably contribute to increase the dissolution of flutamide. Due to the amphiphilic structure of poloxamers, these are developing the micellar core surface area accessible to flutamide molecules. However, different combinations of poloxamers as suppository bases did not show significant influence on the dissolution rates of flutamide from suppositories (Fig. 4).

**Kinetic Modeling of the Release Data** In vitro release study of flutamide-loaded alginate tamarind microparticles and microparticles loaded suppositories showed time independent release of drug. Higher values of ‘$n$’ (>0.89) represent Super Case II-type drug release and suggest that polymer relaxation occurs throughout the entire dissolution period (Table 3). This type of drug transport mechanism is associated with stresses in hydrophilic polymers which swell in water and biological fluids.

**Stability Study** Stability studies were carried out for optimized batch of flutamide-loaded alginate tamarind microparticles as per ICH guidelines. The entrapment efficiency of optimized batch of flutamide-loaded alginate tamarind microparticles after 3 months (91.034%) indicated that the drug was retained within the microparticles throughout the stability period. There was no change in drug content and indicated no significant change in the physical properties. The microparticles remained stable even after exposing to stress conditions of temperature and moisture. Stability studies of suppository showed that there was no significant change in physical characteristics and drug content of suppository after storing 6 weeks at refrigeration temperature.

**Comparison of Plasma Concentration–Time Profiles of Flutamide after Administration of Oral Suspension and Flutamide Tamarind Alginate Microparticles Loaded Suppository** Pharmacokinetics parameters of flutamide after administration of oral suspension and suppository are shown in Table 4. Plasma flutamide levels after oral suspension reached a maximum in about 3 h and then declined rapidly. Plasma flutamide levels after 24 h of administration were as low as 0.4 µg/mL in average. After rectal suppository, plasma flutamide levels reached a maximum in 2–4 h (0.878–1.366 µg/mL in average) and declined slowly. Plasma flutamide levels after 24 h of administration were 0.728 µg/mL in average nearly half of $C_{\text{max}}$. Increased plasma concentration after rectal administration of microencapsulated drug in the form of suppository could be attributed to avoidance of hepatic first pass effect, which was consequence of retaining the drug in the lower rectum i.e., by preventing the upward migration of the suppositories in the rectum by the aid of mucoadhesion. Higher absorption can also reveal the solubility-improving effect of microparticles. Area under curve ($AUC$) for oral suspension and flutamide tamarind alginate microparticles loaded suppository was found to be 15.58 and 18.35 µg·h/mL respectively. This elicits an increase in absorption from suppository than the oral suspension.

**Conclusion** In this study we developed novel poloxamer suppository formulation for prostate cancer therapy by entrapment of flutamide into hydrophilic alginate tamarind microparticles. The developed novel poloxamer suppository gave significantly higher initial plasma concentrations, $C_{\text{max}}$ and $AUC$ of flutamide than oral suspension, indicating that the drug could be more absorbed than that from oral suspension in rats. The developed microparticles loaded poloxamer suppository could be useful formulation for rectal administration of drugs which undergo extensive first pass metabolism or show hepatic side effects and which have low aqueous solubility and poor permeability.

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**Conflict of Interest** The authors declare no conflict of interest.

**References**