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Steady-state pharmacokinetic simulation model of novel pulsatile release dosage form

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Introduction: Bicalutamide, a non-steroidal anti-androgen, has more beneficial properties than the other known anti-androgens, like Flutamide or Nilutamide. It is essentially characterized by a long half- life of about 5.8 days and time to peak plasma concentration of about 31 hours. In clinic, Bicalutamide is generally used for months to years. In view of the same, there is a need for improving the therapy compliance by reduction in the frequency of dosing.

Methods: Tablet dosage form comprising of Bicalutamide was prepared by wet granulation technique, compressed tablets being further coated using functional polymers. A ratio of uncoated minitablets and coated minitablets were filled into hard gelatin capsules corresponding total dose to be administered. In-vitro dissolution drug release profiles were studied using pH change method with buffer pH 1.2, 4.5, and 6.8 containing 1% sodium dodecyl sulfate. Open-label, randomized, fasted, single dose pharmacokinetic study using parallel study design was performed on healthy human volunteers. Five 50 mg Casodex® tablets administered together were used as reference. Blood sampling was done pre-dose and after pre-determined time intervals over one week. Pharmacokinetic parameters were assessed using WINNONLIN® software. Steady-state pharmacokinetics were predicted using SAS software program to determine the parameters after the 85th dosing state. Simulated graphical predictions were also obtained.

Results: The in-vitro drug release profiles indicated a Pulsatile release type product wherein portion of the drug was released immediately and rest was released at higher pH environment (indicating release in lower regions of the gastrointestinal tract). The in-vivo fasting biostudy indicates that the developed formulation has much improved bioavailability as seen in the AUCinf values as compared to innovator product. The steady-state prediction in the pharmacokinetics indicates less fluctuation as compared to innovator product. Less pharmacokinetic variability is observed in the developed formulation as compared to the commercial product. The developed formulation has better absorption, bioavailability and an extended half-life.

Conclusions: Modified release Bicalutamide formulations for oral administration were developed and evaluated for in-vitro and in-vivo performance. Choice of selective excipients allows modification in release profile. The formulation can be formulated as single tablet or as matrix composition. The optimized formulation exhibited 1.5 times absorption as compared to commercial product.