Pharmaceutical Regulatory Affairs 2012: Glass transition temperature (Tg) as a measure of sperm fertility: Effect of antifertility drug nifedipine and its analogues Tata Institute of Fundamental Research, Mumbai

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Abstract

Contraception being the need for the hour, we have synthesized few analogues of nifedipine, an L-type calcium channel blocker and evaluated their effects on sperm fertility. The glass transition temperature (Tg) of spermatozoa has been monitored to characterize the cellular damage due to aging or by external agents. We have shown that the Tg can be used as a marker to measure infertility caused by external agents. The cellular damage can be due to the cell immobilization or due to the membrane alteration ultimately leading to infertility. Results have been supported by measuring the cell motility, metabolism and lipid peroxidation; the well established markers for estimating the sperm fertility. In search of non-hormonal male contraceptives, analogues of nifedipine, which causes reversible infertility, have been synthesized and their interaction at molecular level with model membrane has been probed. Analogues act differently with respect to their antifertility action. This is achieved by altering the cell metabolism thereby directly affecting the motility which is responsible for fertility. Secondly, these drugs bind differently to the interior of the cell-membrane affecting the membrane fluidity, architecture and dynamics. Sulfasalazine and D4 interact to a larger extent and alter the lipid bilayer phase to a hexagonal. D1, D2 and D3 do not have considerable effect. D4 is the most promising candidate as a lead compound for the development of novel non-hormonal male antifertility agents**.**Biodegradable poly(butylene succinate-co-butylene adipate) (PBSA)/poly(hydroxyl ether biphenyl A) (phenoxy) blends have been prepared successfully in this work via solution and casting method using tetrahydrofuran as mutual solvent. PBSA is miscible with phenoxy as evidenced by the single composition dependent glass transition temperature over the whole composition range. Crystallization kinetics Unlike D4, nifedipine and analogue D2 cause sperm cell aging by hampering the motility without causing the membrane damage. This indicates that the damage caused due to D4 may be irreversible. Thus the present findings demonstrate that D2 can be a promising candidate as a lead molecule for the development of reversible antifertility agents. Thus, in an attempt to synthesize non-hormonal, safe, reversible and oral male contraceptive, we have used nifedipine as a prototype molecule. Nifedipine is a calcium channel blocker and popular anti-hypertensive drug. Its reversible anti-fertility effect is a well-known side effect. In order to develop male oral contraceptive, we have synthesized four analogues; m-hydroxy (D5), m-chloro (D6), p-nitro (D7), p-methoxy (D8) aryl 1, 4-dihydropyridine derivative of nifedipine and monitored their effect on sperm motility and metabolic activity. To highlight their mechanism of action on sperm function through membrane interaction, we have studied their molecular level interactions with model membrane using NMR and DSC technique. One of the synthesized analogues (D5) showed promising results.