Trazodone Hydrochloride (TZN), a serotonin uptake inhibitor, is used in the treatment of moderate to severe depression in schizophrenic patients. The undesirable side effects of TZN administered orally can be offset using the transdermal route, which attenuates the fluctuating TZN levels (52 - 81 %) resulting from oral therapy. The present study report the biopharmaceutical behaviors of matrix patch containing TZN following transdermal administration in rabbits. The TZN transdermal patch was prepared by solvent casting technique using Eudragit RL 100 and RS 100 polymers along with triethylcitrate (plasticizer) and fennel oil (permeation enhancer). The ex vivo skin permeation study was performed using Keshary-Chien transdermal diffusion cell and human cadaver epidermis with intact stratum corneum as membrane. TZN patch was applied to the inner pinna skin of the rabbit and transdermal absorption from patch was compared to that from peroral TZN solution in rabbit. A steady-state skin permeation rate of 135.75 ± 1.18 µg/cm²/h was achieved from the matrix patch across human cadaver epidermis after an initial lag time of ~3 hours. The steady-state transdermal TZN concentration of 2.3 µg/ml was achieved in rabbit from the matrix patch after an initial lag time of ~2 h. The Cmax of peroral TZN solution was calculated to be 5.84 µg/ml at a Tmax of 2 h indicating its rapid absorption compared to the transdermal administration with a Tmax of 5 h. The peroral and transdermal TZN bioavailability in rabbit are calculated to be 19 % and 32 %, respectively. The ex vivo and in vivo biopharmaceutical parameters were in good agreement with respect to input rate, steady-state plasma TZN concentration and lag time. The transdermal dose achieved a much higher steady-state blood concentration in rabbit compared with the effective blood concentration in human. The observed steady-state blood concentration may appear to be within the expected therapeutic range in human with a higher clearance value compared to that in rabbit. It can be estimated that a transdermal patch of about 40 cm² containing 4 mg/cm² of TZN is likely to be able to attain and maintain therapeutic concentration (0.75 µg/ml) of TZN over a period of 24 hours and even further.