The Alg–5FU nanoparticles were prepared using a spray drying technique;5FU can be encapsulated in the matrix of the polysaccharides via bonds with functional groups in the alginate chain [31].Hence, the frequency of the dosage regimen, patient compliance and continuation of treatment for long time could be enhanced markedly by using 5FU–Alg–Np–HG.Hence, the frequency of the dosage regimen, patient compliance and continuation of treatment for long time could be enhanced markedly by using 5FU–AlgNp–HG.The release profile of 5FU from the nanoparticles and hydrogel was investigated in phosphate buffer pH 5.5 (in–accordance with skin pH) and phosphate buffer pH 7.4 (in–accordance with blood pH) at a temperature 32 oC (inaccordance with skin temperature) and 37 oC (in–accordance with blood temperature), The release of drugs from polymeric materials can be controlled by a number of physical processes respectively(Figure6a,b).Thesimple5FUsolution(inphosphatebufferpH7.4)withouta carrierwasalsoexploredasareference.Theresultsshowthatdrugsolutionreleases5FU upto97%in6h.Alginatenanoparticlessignificantlysloweddown/controlthereleaseof 5FUascomparedtosolution(ANOVA;p0.05) (Figure 7b).matrix–forming polymer was also previously used for topical hydrogel formulations due to its permeation enhancer properties.Findings from our study reflect an important indication on the in–vivo sustained performance of hydrogels (5FU–Alg–Np–HG) after single application.Findings from our study reflect an important indication on the in–vivo sustained performance of hydrogels (5FU–Alg–Np–HG) after single application.The highly negative zeta potential induced repulsion between nanoparticles, greatly reducing the propensity to aggregate and making the nanoparticles highly stable in an aqueous solution [35].We found that 5FU has the characteristic peaks at 2992 (N–H stretchThe 5FU solution and 5FU–Alg–Np–loaded chitosan–gelatin–based hydrogels were prepared.We found that 5FU has the characteristic peaks at 2992 (N–H stretching vibrations), 2883 (C=H stretching vibrations), 1723 (C=O group of ketone), 1505 and 1253 cm−1 (stretching vibration of C=N and C=F, respectively) [38].It was observed that the hydrogel became turbid at body temperature in comparison to the initial sol Rheological analysis can provide information regarding the ability of gel formulations to spread on the skin.However, when comparing nanoparticles vs. hydrogels, it was found that the permeability of 5FU was weaker when incorporated in gel.Particle size and zeta potential are the principal criteria for evaluating effective anticancer drug delivery targeting tumor tissue [32].Studies have shown that nanoparticles in the size range of 20–200 nm have the maximum retention in the tumor cell [33].The particle size of the prepared nanoparticles was determined in an aqueous solution.F. Code Size (nm) Zeta Potential The 5FU solution and 5FU–Alg–Np–loaded chitosan–gelatin–based hydrogels were prepared.The absorption peaks of nanoparticles and 5FU were weaken in FTIR spectrum of hydrogels (Figure 2).The absorption peaks of nanoparticles and 5FU were weaken in FTIR spectrum of hydrogels (Figure 2).The polymers, i.e., alginate and chitosan, are the main components of nanoparticles and hydrogels, play a role in determining drug permeation.The stratum corneum, the outermost layer of skin, has highly organized structure and is main barrier and hence hinders drug penetration.The polymers, i.e., alginate and chitosan, are the main components of nanoparticles and hydrogels, play a role in determining drug permeation.Skin–related drug retention was significantly higher when 5FU–Alg–Np–HG was applied on the rats skin (ANOVA, p0.05).Skin–related drug retention was significantly higher when 5FU–Alg–Np–HG was applied on the rats skin (ANOVA, p0.05).The results show that there is no drastic

change in pHvalue after conversion of sol to gel, confirming that there is no undesired chemical reaction in the system.Visual evaluation of the prepared hydrogel was performed at different temperatures (i.e., 25–37 oC) for the assessment of transparency.Swelling Studies Swelling is described as a phenomenon in which water and/or biological fluids are retained in a polymer network.Swelling ability of the prepared hydrogels was evaluated by monitoring the mass changes during incubation in the dissolution medium.The permeation of 5FU across the skin was higher in the case of nanoparticles as compared Gels 2022, 8, x FOR PEER REVIEW to hydrogels (ANOVA, p0.05) (Figure 7a).Alginate and chitosan both interact with skin components proteins and lipids and helps in drug permeation.Chitosan reversibly fluidizes the skin lipids and proteins, which results in the permeation of 5FU [45].Alginate and chitosan both interact with skin components proteins and lipids and helps in drug permeation.This was due to the presence of polymer alginate in 5FU–Alg–Np–HG.2.2.1.2.2.1.2.2.2.2.2.5.3.2.4.11 of 17 2.5.