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Preparation and Characterization of Iguratimod Oral Formulation Using IPNs of Carboxymethyl Tamarind Seed Gum and Cyclodextrin Nanosponges

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Abstract In the present study, Iguratimod-loaded Cyclodextrin Nanosponges and carboxy methyl tamarind gum interpenetrating polymer networks (IPNs) based tablets were prepared to improve bio-pharmaceutical properties. By varying the concentration of carboxymethyl tamarind gum and glutaraldehyde as cross-linker, Iguratimod-loaded IPNs of formulations (T1-T5) were prepared by freeze-drying, characterized for FTIR, DSC, and XRD and evaluated for % drug loading, equilibrium swelling. Drug-loaded IPN tablets were prepared using Avicel PH-102 and performed in-vitro and in-vivo evaluation studies. The drug load in the IPNs varied between 61.43% and 66.57%, and swelling in the 0.1N HCl presence was significantly less than in the pH 6.8 phosphate buffer. Research employing XRD, DSC, and FTIR confirmed the formation of a molecular complex between Iguratimod and IPNs. The hardness, thickness, mean weight, friability, and average percentage drug content for Iguratimod-loaded IPN tablets were all within limits. Sustain release of drug was observed with IPN tablets in an In-vitro drug release study. In-vivo studies in rabbits estimated various pharmacokinetic constraints $AUC_{0-\infty}$, AUC_{0-t}, Cmax, Tmax, and MRT. The $AUC_{0-\infty}$, $t_{1/2}$, and MRT values of optimized formulations were pointedly more than those with pure drug and commercial tablets. Thus, related to the pure drug and the marketed product, the study's findings showed increased bioavailability and controlled release of Iguratimod from the optimized IPN tablet formulation.

Keywords Iguratimod, Carboxy Methyl Tamarind Gum, Interpenetrating Polymer Networks, Cyclodextrin-Nanosponges, IPN Tablets

1. Introduction

For the recent few decades, an ever-growing demand for upgrading the properties of polymers has cemented the development of the blending of polymer mixtures.

Interpenetrating polymer networks (IPNs), a novel drug delivery approach, have significant advantages for targeted and regulated drug delivery. These advantages include better loading capacity, mechanical strength, biocompatibility, stability, high swelling capacity, and biodegradability. IPNs have two distinguishing characteristics that set them apart from other forms of polymeric blends: (1) they swell but do not dissolve in solvents, and (2) they have suppressed creep and flow [1]. IPNs are synthesized to combine individual properties of polymers, indicating that a combination or mixture of polymers can be employed successfully as drug delivery systems. Natural and synthetic polymers are widely used to

prepare IPNs [2].

Novel hyper-crosslinked synthetic polymers called cyclodextrin nanosponges are solid nanoparticles with colloidal diameters and nanosized voids [3,4]. The primary crosslinking substances used to create these nanosponges are active carbonyl substances, including triphosgene, carbonyl diimidazole, and diphenyl carbonate; the resulting nanosponges display carbonate bonds between two cyclodextrin monomers. The surface tension of water is not appreciably changed by cyclodextrin nanosponges. Due to their non-hygroscopic nature, they maintain their structure when absorbing and releasing moisture [5]. The rigid structure and insoluble nature of these nanosponges may restrict the effective utilization of this novel polymer. To enhance the characteristics of cyclodextrin nanosponges, we concentrated on developing IPNs based on carboxymethyl tamarind seed gum.

IPNs are produced using tamarind gum, a natural polymer that is combined with various synthetic polymers. It is an inexpensive, environmentally friendly, and neutral polysaccharide obtained from the endosperm of Tamarindus indica L. seeds, a member of the Leguminosae family. It is native to Southeast Asia, Africa, and India [6]. Carboxymethyl tamarind gum is an anionic polymer with lesser biodegradability and enhanced hydration, viscosity, and swelling. Therefore, releasing retardant substances in drug delivery may be beneficial [7]. The novel carboxymethyl tamarind gum-g-polyacrylonitrile hydrogel has been mentioned in literature as an adsorbent for diaper application [8].

Iguratimod was discovered by Toyama Pharmaceuticals in 2012 for the treatment of rheumatoid arthritis. T and B lymphocyte suppression, as well as other pro-inflammatory cytokines, are the part of its action. Additionally, promoting osteoblast growth and repressing osteoclast genesis had anabolic effects on bone metabolism. The drug is only taken orally and shows practical insolubility in aqueous solutions. Numerous factors affect the rate and extent of medicine intestine absorption, which has a negative impact on clinical efficacy and increases GIT adverse effects. A novel formulation is needed to reduce adverse therapeutic effects and improve its absorption to achieve a promising treatment of RA [9]. The development of IPNs of Iguratimod employing CMTG and cyclodextrin nanosponges (CDNS) was attempted in light of the above-mentioned information. The prepared IPNs were characterized and compressed as tablets using Avicel PH-102 and performed in-vitro and in-vivo assessment studies.

2. Materials and Methods

Iguratimod was gifted from Dr. Reddy's Laboratory Ltd. in Hyderabad, India. CDNS16 created in our lab were employed for this research. CMTG was given by the Hyderabad, India-based company Tamarind Magic. A glutaraldehyde solution (25% aqueous) was acquired from Sigma Aldrich in Milan, Italy. The other reagents and substances used in this investigation were all analytical grade. Marketed tablet of Iguratimod was purchased from the local market.

2.1. Preparation of IPNs of Iguratimod

Lyophilization was used to make Iguratimod-loaded interpenetration polymer networks, with a small modification of the procedures previously reported [10-12]. Five batches of formulations were formulated by altering the concentration of CMTG, as shown in Table 1. 50 ml of Milli Q water was mixed with precisely weighed amounts of CMTG and drug using a magnetic stirrer. A mechanical stirrer (REMI) was used to uniformly distribute CDNS in 50 ml of water. Both mixtures were added slowly and kept under 10 minutes of sonication for aggregation prevention. At every two-minute interval for 10 min, a measured quantity of aqueous glutaraldehyde (GA) was added. This mixture was then continuously stirred for the following 24 hours. To isolate the un-complexed drug and other reactants, for 10 minutes, it was centrifugated at 5000 rpm, and the colloidal supernatant was separated and lyophilized. The resultant dry powder was desiccated after lyophilization. A blank batch of IPNs was also prepared without loading drug.

Table 1. Preparations of Iguratimod-loaded IPNs [13]

Preparation	CDNS16 %w/v	CMTG %w/v	Iguratimod %w/v	GA (ml)
T0	0.5	0.6	0	1
T1	0.5	0.6	0.5	1
T2	0.5	0.6	0.5	2
T3	0.5	0.6	0.5	3
T4	0.5	0.4	0.5	1
T5	0.5	0.8	0.5	1

2.2. Determination of Iguratimod Loading in IPNs [13]

Iguratimod-loaded IPNs were accurately weighed (100mg), then dissolved in methanol, and sonicated for ten minutes. Next, the volume in the volumetric flask was adjusted to 100 ml using a pH 6.8 phosphate buffer. Iguratimod concentration was evaluated by means of a UV-Visible spectrophotometer at 244 nm. The percentage drug load was calculated using the following equation (1).

$$\% \text{ Drug loading} = \frac{\text{Drug load weight in IPN Formulation}}{\text{Starting weight of the drug used for loading}} \times 100 \quad (1)$$

2.3. Physicochemical Analysis of Iguratimod-loaded IPNs [13,14]

2.3.1. Fourier Transformed Infrared (FTIR) Spectroscopy

Tensor 27 FTIR Spectrophotometer (Bruker Optics, Germany) was used to measure the FTIR spectra of Iguratimod, CDNS, CMTG, blank IPNs, and Iguratimod loaded IPNs between 4000 and 600 cm^{-1}.

2.3.2. Differential Scanning Calorimetry (DSC)

DSC was carried out on Iguratimod, CDNS, CMTG, Blank IPNs, and Iguratimod-loaded IPNs utilizing an instrument controller (TAC 7/DX, Perkin-Elmer, CT-USA). The temperature range of 30 to 400°C was used, and the heating rate was 10°C per minute. Five milligrams' samples were subjected to analyses in triplicate while being nitrogen-purged.

2.3.3. X-Ray Powder Diffraction (XRD)

The XRD patterns of Iguratimod, CDNS, CMTG, Blank IPNs, and Iguratimod loaded IPNs in the 2θ range 2.5° to 60° field were obtained using the Bruker D8 Advance X-ray diffractometer. The crystallinity index was computed using equation (2):

$$\text{Crystalline Index (\%)} = \frac{\text{Area under the crystalline peaks}}{\text{Area under all peaks}} \times 100 \quad (2)$$

2.3.4. Equilibrium Swelling

A known quantity (100 mg) of IPNs was added to 100 ml each of phosphate buffer pH 6.8 and 0.1N HCl, and they were left to swell for 24 hours at room temperature. After a 24-hours, IPNs were reweighed after any extra water had been wiped using filter paper. The equilibrium swelling index of batches that had been developed was finally computed using an equation (3):

$$\text{Equilibrium Swelling (\%)} = \frac{\text{weight of swollen IPNs} - \text{weight of dry IPNs}}{\text{weight of dry IPNs}} \times 100 \quad (3)$$

2.4. Preparation of Iguratimod Loaded IPN Tablets

In a mortar, precisely weighed amounts of Iguratimod-laden IPNs (equivalent to 25 mg Iguratimod) and the computed amount of Avicel PH-102 (added up to 300 mg) were mixed with pestle for two more minutes. The finished mixes were compressed as tablets with a tablet machine (8 mm round, flat-faced single punch).

2.5. Evaluation of Tablet Formulations [13,15,16]

According to reported techniques, prepared tablets were evaluated for various factors, including uniformity of weight, content uniformity, hardness, friability, and disintegration time.

2.5.1. In-Vitro Release Study of Iguratimod Loaded IPN Tablets

Iguratimod-loaded IPN and commercial Iguratimod tablets were examined in-vitro using type-I USP dissolving test equipment (Electrolab TDT-06P, India). The release of the drug was observed for the first two hours in 900 ml of an acidic medium (pH 1.2) and then for the remaining eight hours in a medium with a pH of 6.8 at 37°C. To measure the percentage of drug release, samples were removed and diluted adequately at predefined time intermissions (0, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 h). Three duplicates of the experiment were performed.

2.6. Pharmacokinetic Studies of Iguratimod Loaded IPN Tablets

The in-vivo pharmacokinetic investigation was authorized through the institutional animal ethics committee (IAEC NO: 1447/PO/Re/S/11/CPCSEA-56/A) and was completed according to the ethical guidelines for laboratory animal studies. 18 New Zealand white rabbits weighing 4-5 kg of either sex were recruited for this investigation. After that, they were separated into Groups I, II, and III. The rabbits in Group I received only pure drug, Group II received an Iguratimod-marketed tablet, and Group III received an Iguratimod-loaded IPN formulation (dose equivalent to rabbit dose - 4.218 mg) [17].

Blood (1 ml) was collected with syringes from the marginal ear vein, and blood samplings continued at intervals 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 14, 16, 20, and 24 hours after study drug administration. The samples were vortexed for 120 seconds after being deproteinized with acetonitrile. It was further centrifuged at 4000rpm for 4 min, and the supernatant liquid was separated and stored in a freezer (-20°C) until assayed.

2.6.1. Apparatus and Chromatographic Conditions

An Agilent Technologies Series 1200 HPLC with a UV detector (Agilent Technologies, Palo Alto, CA, USA) was used for the HPLC analysis. Chromatographic separations were carried out at 25°C with a reversed-phase Security Guard C18 guard column and an Alltima C18 column (5 µm, 250× 4.6 mm i.d., Alltech Associates Inc., USA). The mobile phase contained a 40:60 (v/v) acetonitrile-acetic acid aqueous solution with a pH of 4.5. The detecting wavelength was set at 257 nm, and the flow rate was 1 ml/min. The Agilent-provided HP Chemstation software (version B.02.01) was utilized to record and analyze the chromatographic data [18].

2.6.2. Pharmacokinetic (PK) Parameters

Maximum plasma concentration (Cmax), Tmax, i.e.,

time to reach Cmax, elimination half-life ($t_{½}$) values, and the area under the plasma concentration-time curve from zero to the last sampling time (AUC_{0-t}), area under the plasma concentration-time curve from zero to infinity ($AUC_{0-\infty}$), and Mean residence time (MRT) were the pharmacokinetic parameters used to evaluate.

3. Results and Discussion

In the present study, crosslinked cyclodextrin polymer was employed as a base polymer. It was further crosslinked with glutaraldehyde to form a network, while the second polymer, crosslinked carboxymethyl tamarind gum, gets entangled in the cavities of crosslinked cyclodextrin nanosponges. It was predicted that secondary hydroxyl groups of carboxymethyl tamarind gum may get crosslinked with glutaraldehyde. The second polymer may get entangled in the cyclodextrin nanosponges due to the creation of a composite between the free hydroxyl moiety of nanosponges and the carboxyl group of carboxymethyl tamarind gum. IPNs were prepared in five batches by the lyophilization process. As given away in Table 2, the percentage of drug entrapping in the IPN complex was between 61.43 to 66.57 %. Due to the high glutaraldehyde concentration, a high drug loading efficiency was observed with the formulation(T3). When the concentration of glutaraldehyde increased, it was found that the efficiency of drug entrapment increased significantly p.

Table 2. Drug loading percentage in IPNs

S.NO	Name of the preparation	% Drug loading
1	T0	61.43
2	T1	64.12
3	T2	66.57
4	T3	63.17
5	T4	64.18

The FTIR spectra of CMTG, CDNS16, Iguratimod, and Iguratimod-loaded IPNs are compared in Figure 1. The stretching vibration of the -OH groups (of glucose, xylose, and galactose units of the gum) was indicated by significant peaks in the FTIR spectra of CMTG at 3421.83, 3443.05, and 3524.06 cm^{-1}. A significant peak at 1058.96 cm^{-1} is caused by the C-O stretching vibration of the alcoholic group. The medium peaks at 2854.74 cm^{-1} and 2924.18 cm^{-1} revealed the asymmetric stretching of CH. The C=O group of ester is responsible for the peak's existence at 1745.64 cm^{-1}. The existence of carboxyl moiety in CMTG was indicated by the peaks at 1637.62 cm^{-1} and 1400.37 cm^{-1}. The distinctive peak in the FTIR spectra of CDNS was observed at 1740–1750 cm^{-1}, indicating the presence of a carbonate bond among two molecules of β-CD. Furthermore, the C-H stretching vibration of 2918 cm^{-1}, the C-H bending vibration of 1418 cm^{-1}, and the C-O stretching vibration of 1026 cm^{-1} of primary alcohol were identified as the additional distinguishing peaks of NS. Blank IPNs spectra had all representative peaks of both NS and CMTG along with developing new peaks at 1720 cm^{-1} and 1028cm^{-1} implicative of carbonyl group linkage formation between GA and CDNS and an acetal linkage formed due to the reaction of hydroxyl (–OH) group of CMTG with aldehyde (-CHO) group of GA respectively. Crosslinking of CDNS and CMTG by GA confirmed this. Further, in the case of blank IPN, the –OH stretching vibration broadening suggests the intercalation of polymeric chains owing to strong intermolecular interactions together with hydrogen bonding of CMTG and NS. The distinctive peaks of Iguratimod were seen in the FTIR spectra of pure Iguratimod, which were located at approximately 3423, 3347, 3276, 3123, 3065, 2869, 1687, 1620, 1592, 1531, 1487, 1425, 1358, 1342, 1264, 1210, 1155, 970, and 757 cm^{-1}. Iguratimod's distinctive peaks were observed in drug-loaded IPNs with minimal shifting and intensity reduction. A more significant frequency shift in the C=O stretching vibration peak indicates the hydrogen bonding.

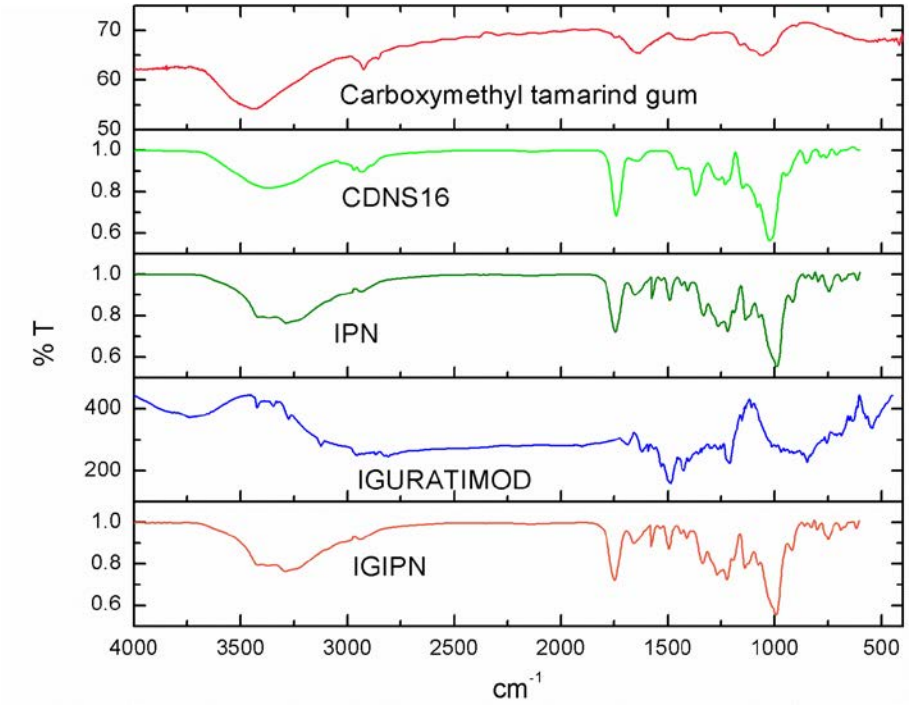

Figure 1. FTIR spectra of CMTG, CDNS16, Blank IPN, Iguratimod and Iguratimod loaded IPN

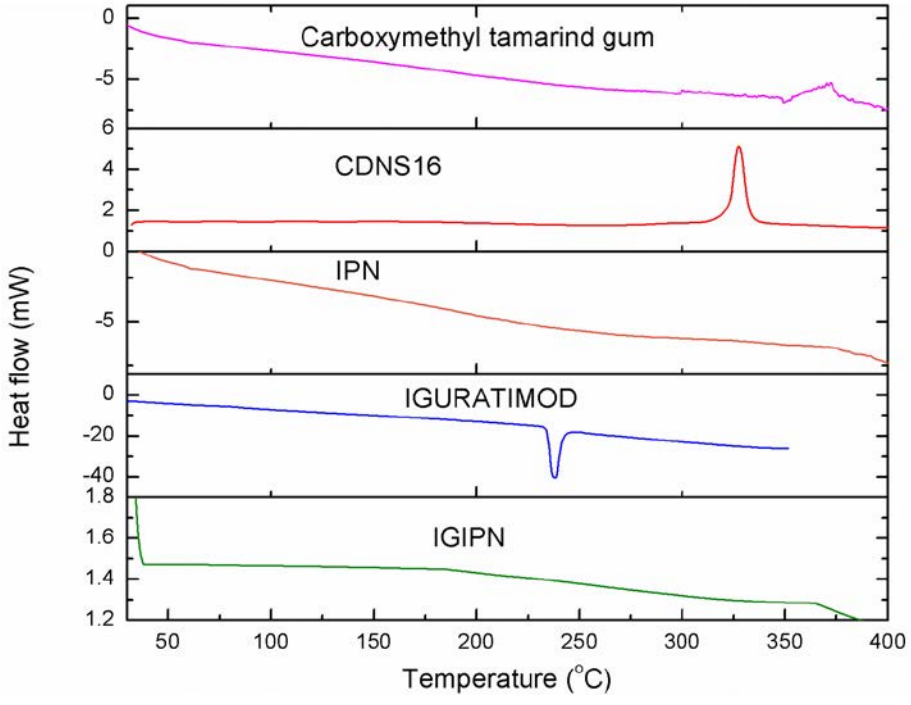

Figure 2. DSC thermograms of CDNS, plain IPN, Iguratimod, and Iguratimod-laden IPN, Carboxymethyl tamarind gum

Differential scanning calorimetry curves of the CDNS16, CMTG, blank IPNs, Iguratimod, and Iguratimod loaded IPNs are displayed in figure 2. Exothermic peak was visible on the CDNS16 DSC thermogram at about 350°C. At about 372°C, CMTG showed an exothermic peak. IPN's DSC curve did not exhibit a recognizable peak. The nonappearance of distinct peaks for either separate polymer in IPN indicates that a crosslinked polymeric structure was created by the intercalation of polymeric chains of CMTG and CDNS. Iguratimod, a free drug, has a prominent endothermic peak on the DSC thermogram at about 238.51°C, indicating the substance is crystalline. Drug-loaded IPN complexes have not displayed any typical drug and individual polymer peaks. This may be evidence that Iguratimod has amorphized within the internal polymer network.

As shown in Figure 3, the X-ray diffractograms of plain Iguratimod showed different peak intensities at 2θ values of 6.88°, 10.92°, 17.54°, 19.56°, 20.8°, 24.56°, and 26.00°, and crystallinity index 87.75% showing the drug's crystalline form. However, the IPN complex did not show a typical peak of pure Iguratimod, and also its crystallinity index found to be 21.35% which is similar to that of blank IPNs (20.43 %). The lack of Iguratimod's crystalline peaks in the IPN complex and crystallinity index values suggests that the drug has amorphized across the IPNs' polymer network. The formation of a molecular complex between Iguratimod and IPNs was confirmed by FTIR, DSC, and XRD testing.

The formulation in 0.1N HCl has a low ($P<0.05$) swelling compared to that in phosphate buffer pH 6.8. CMTG is present in an acidic medium in unionized state with pH of 0.1N HCl being below the pKa of carboxyl groups (-COOH) on CMTG that results in decrease in electrostatic repulsion owing to protonation of -COOH groups. This results in decreased water uptake by IPN due to prevention of swelling. Also, the equilibrium swelling was found to be proportional to CMTG concentration in IPN, as depicted in figure 4, which might be attributed to CMTG hydrophilic nature. High swelling values for the T5 formulation may be caused by the deprotonation of -COOH groups, which led to ionization and electrostatic repulsion of ionized carbonyl groups, further increasing polymer mobility and improving network mesh size. An increase in glutaraldehyde concentration in IPN decreased the equilibrium swelling (T1-T3). The T3 has a very low swelling owing to high IPN's cross linking density that reduced mobility, relaxation and polymer chains expansion. These results are a clear indication of pH dependent swelling of CMTG and CDNS IPNs that are suggestive of site-specific oral drug delivery by prevention of drug release in an acidic gastric environment.

The determined average weight, hardness, thickness, percent friability, and percent drug content values of formulated IPN tablets are given in Table 3.

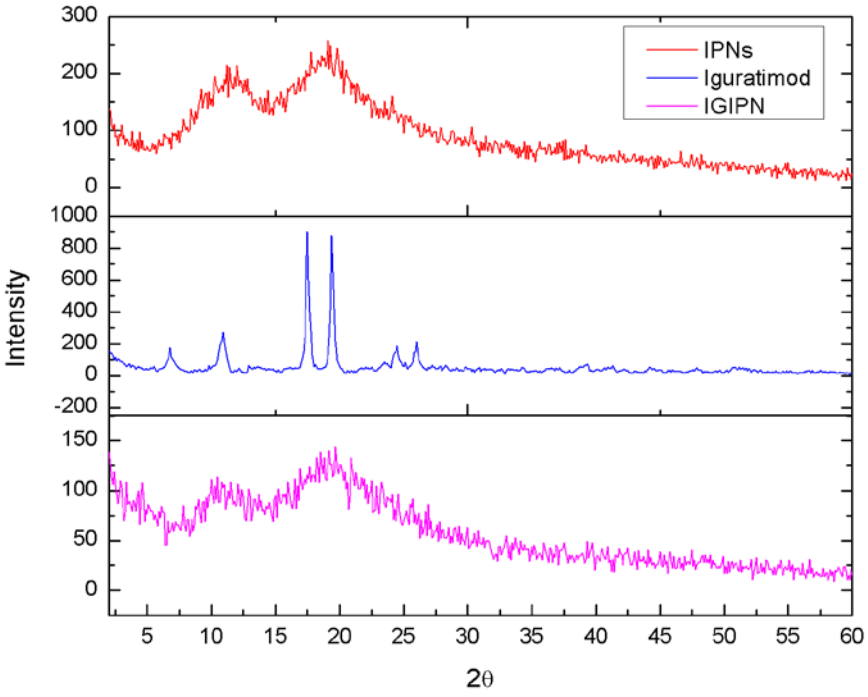

Figure 3. X-ray diffractograms of plain IPNS, Iguratimod and Iguratimod laden IPNS

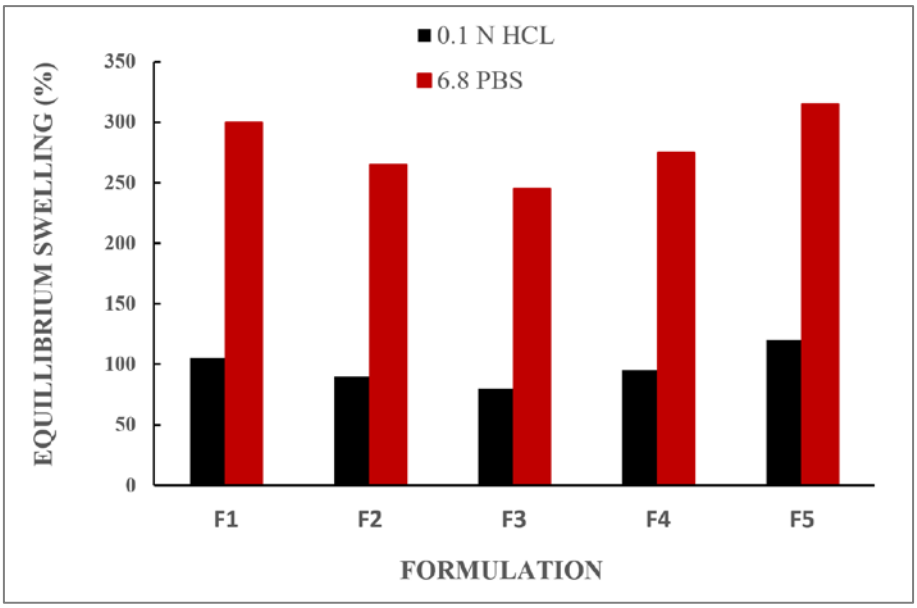

Figure 4. IPNs' equilibrium swelling (%) in a pH 6.8 phosphate buffer and 0.1N HCl

Table 3. Evaluation parameters of Iguratimod loaded IPN tablets

Tablet Preparation	Weight (mg)	Thickness (mm)	Hardness (kg/cm^2)	% Friability	% Drug content
T0	299.63 ± 1.58	4.94 ± 0.28	5.24 ± 0.22	0.27 ± 0.05	99.47 ± 1.28
T1	300.53 ± 2.08	4.89 ± 0.36	5.16 ± 0.34	0.24 ± 0.07	99.34 ± 2.87
T2	301.14 ± 3.06	5.06 ± 0.18	5.33 ± 0.12	0.31 ± 0.08	99.88 ± 1.76
T3	298.82 ± 1.12	5.12 ± 0.24	5.18 ± 0.19	0.28 ± 0.04	99.58 ± 1.43
T4	300.12 ± 0.96	4.92 ± 0.32	5.45 ± 0.17	0.28 ± 0.03	99.62 ± 2.10

Iguratimode drug release from prepared IPN tablets showed a biphasic pattern. When compared to drug release in pH 6.8 medium, it was found that the percentage of drugs released in an acidic medium (pH 1.2) from the IPN tables was lower. This may be due to the low swelling of IPNs in an acidic environment, which retains the drug release from IPNs. The release ranged from 14.34 %±2.23 to 15.87 %±1.34 (at the end of 2hrs of the release study in an acidic medium), tailed by controlled release of the drug in simulated intestinal medium (pH 6.8) for 12 hrs. After nine hours, the amount of drug released from prepared tablets ranged from 86.34%±1.67 to almost 98.85%±1.12. The commercial tablet showed the complete drug release within two hours, as shown in Figure 5. The formulation T3 was deemed to be an optimized formulation based on the findings of this dissolution investigation since it sustains drug release more effectively than any other formulation.

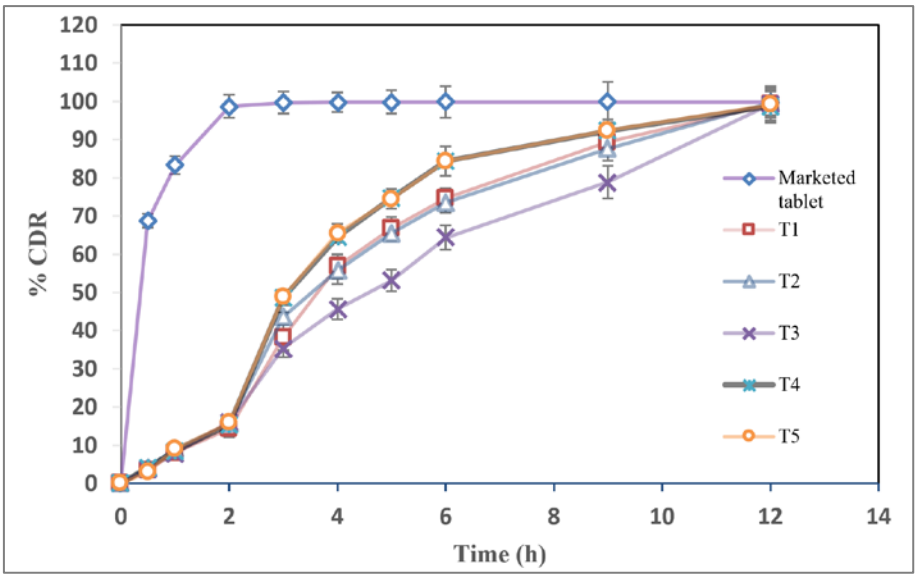

Figure 5. In-vitro dissolution profile of Iguratimod IPN tablets and commercial tablet

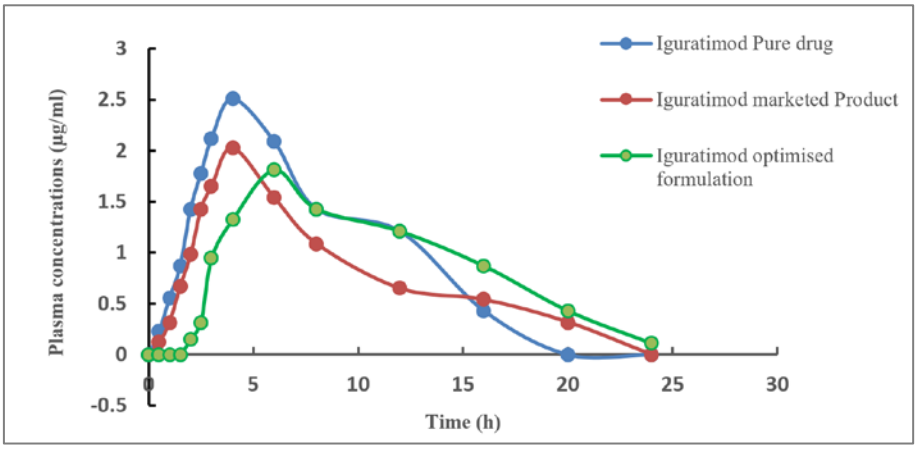

Figure 6. Plasma concentration-time profiles for Iguratimod pure drug, Commercial formulation, and Iguratimod IPN tablet in rabbits.

Figure 6 illustrates the plasma concentration-time profile in rabbits after a single oral dose of the Iguratimod-loaded IPN preparation, compared to commercial tablets and pure drug suspension.

Cmax of the Iguratimod marketed product, and IPN optimized Formulation 2.03±0.32 and 1.81±0.14 µg/ml was substantial relative to the pure drug suspension 2.51±0.32µg/ml. Tmax of marketed T3 tablets and the plain drug was 4.00±0.02, 4.00±0.04, and 6.00±0.09h, respectively. $AUC_{0-\infty}$ for marketed and T3 tablets was (6.82±1.49 and 7.57±1.68µg.h/ml) higher than the plain drug suspension (5.71±1.27µg.hrs/ml). High drug concentrations in the systemic circulation compared to pure drug solution formulation can suggest enhanced systemic drug absorption. Higher drug concentrations in plasma with optimized IPN tablets revealed the improved bioavailability of Iguratimod from IPN tablets as related to the plain drug and marketed product. The higher $t_{½}$ (7.51±0.06 hrs) and MRT (8.15±0.15) values of optimized tablets as compared to pure drug and marketed formulations indicate the sustained release of drug from prepared optimized formulation (Table 4).

Table 4. PK parameters of Iguratimod plain drug, commercial tablet and Iguratimod optimized IPN formulation in rabbits

PK parameters	Iguratimod Plain drug	Iguratimod– commercial product	Iguratimod Optimized Tablet
C_{max} (µg/ml)	2.12±0.32	2.03±0.32	1.81±0.14
AUC_{0-t} (µg. h/ml)	4.43±0.51	4.73±0.63	5.94±0.86
AUC_{0-inf} (µg. h/ml)	5.71±1.27	6.82±1.49	7.57±1.68
T_{max} (h)	4.00±0.02	4.05±0.04	6.00±0.09
$t_{1/2}$ (h)	4.36±0.02	4.79±0.09	7.51±0.06
K_{el}	0.158±0.004	0.1445±0.004	0.092±0.0001
MRT(h)	5.14±0.14	5.42±0.24	8.15±0.15

4. Conclusions

Successfully the interpenetrating networks of CMTG and CDNS were fabricated. CMTG and CDNS have the ability to form the polyelectrolyte complex due to electrostatic attraction between the -COO- a group of CMTG and –OH groups of CDNS. FTIR, DSC, and XRD studies revealed the cross-linking of CDNS and CMTG by glutaraldehyde and amorphization of the drug in the internal polymer network. Iguratimod IPN-based tablets were prepared and evaluated, and it was observed that the IPN tablets sustained drug release compared with commercial tablets. In vivo pharmacokinetic studies revealed that during the first two hours, low plasma drug concentrations with optimized formulations were observed compared with marketed formulations and pure drug, revealing that the optimized formulation retarded the release of drug in the stomach may be owing to IPN's low degree of swelling in an acidic environment. The pharmacokinetic parameters $AUC_{0-\infty}$, $t_{1/2}$, and MRT values of optimized formulations were significantly more than those with pure drug and commercial tablets. The study's results thus demonstrated higher bioavailability and controlled release of Iguratimod from the optimized IPN tablet formulation when related to the pure drug and the commercial product.

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