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Original Article

Formulation and Characterization of Inter-Penetrating Network of Isabgol Husk Mucilage for Modified Release of Diclofenac Sodium

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ABSTRACT

Introduction: Diclofenac Sodium (DS), a Non-Steroidal Anti-Inflammatory Drug (NSAID) is widely used in inflammation and pain management. However, the drug has a short half-life of 1.2-2 hr therefore, frequent administration of DS is required. In this research paper Inter-Penetrating Network (IPN) microspheres of Diclofenac sodium were made using Isabgol husk mucilage and Polyvinyl Alcohol (PVA) to prolong the release of diclofenac sodium. Isabgol husk is widely explored as a natural, economical, biocompatible, and biodegradable polymer for the development of a modified-release drug delivery system. **Materials and Methods:** IPN microspheres were prepared using Isabgol husk mucilage and Polyvinyl alcohol by emulsion cross-linking method in the presence of DL glyceraldehyde as a cross-linker. **Evaluation:** Fourier Transform Infrared (FTIR) spectroscopy was performed to confirm the formation of an interpenetrating network. The chemical stability of the drug and its molecular dispersion in the IPN was validated by X-ray Diffraction (XRD) analysis. The prepared microspheres were evaluated for % yield, drug loading, entrapment efficiency, surface morphology, swelling index and *in vitro* drug release. **Results:** The percentage yield and drug entrapment efficiency of the formulations were found in between 66.33 to 95.345%, and 40.24 to 68.12% respectively. The SEM and light microscopy studies confirmed the formation of spherical IPN microspheres. The model kinetics of *in vitro* release data found Korsmeyer-Peppas as the best-fit model for drug release from IPN microspheres.

Keywords: Inter-Penetrating Network, Isabgol husk mucilage, Diclofenac Sodium, DL-glyceraldehyde, Polyvinyl Alcohol.

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INTRODUCTION

Polymers have always been useful excipients in both conventional and novel drug delivery systems. Natural as well as synthetic polymer can perform complex and advanced tasks like controlled release of drugs, drug targeting and development of various novel drug delivery systems. Natural polymers are very popular for designing novel drug delivery systems because of their cost-effectiveness, biodegradability, biocompatibility, non-toxicity, and flexibility in desirable drug release profiles.[1] However, these natural polymers have some limitations in processability and reactivity. Therefore, to overcome these shortcomings and to improve mechanical strength, a new class of polymer was developed on the basis of blending or crosslinking either of natural or synthetic polymer alone or together.[2]

An Interpenetrating Polymer Network (IPN) is a mixture of two or more polymers in which one of the polymer systems is synthesized in the presence of another, resulting in the formation of a physically cross-linked network. Each polymer network retains its characteristics, resulting in cumulative improvements in characteristics like strength or toughness. An IPN can be differentiated from a polymer blend since it swells but fails to dissolve in solvents and suppressed creep and flow deformations.[3,4] They differ from polymer complexes and graft copolymers as well, which either involve chemical bonding and a limited degree of cross-linking. IPN can be broadly referred to as "polymer alloys", allowing polymer blends to obtain the pertinent morphology by making them chemically compatible. IPN has gained considerable attention over conventional polymers in the pharmaceutical field especially in controlled drug delivery systems because of its non-toxic, biocompatibility and biodegradable polymer network.[5,6]

Several strategies have been developed for IPN based drug delivery including microspheres, hydrogels, nanoparticles, tablets etc. to target specific sites and control drug release. IPN

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microspheres are considered as flexible carriers for controlled and targeted drug release because of their capacity to encapsulate a broad variety of drugs, resulting in enhanced bioavailability, biocompatibility, reduced toxicity, and controlled and sustained release properties.[6]

Diclofenac Sodium (DS), is NSAID used in muscular pain and arthritis-related swelling, inflammation, and joint pain. The drug has a short half-life of 1.2-2 hr therefore, frequent administration of DS is required. It acts by inhibiting cyclooxygenase-I and II (COX-1 and COX-2) enzymes responsible for prostaglandin production.[7]

Repeated administration of DS reported several effects of cardiovascular risk such as Myocardial Infarction (MI), heart failure, stroke and these risks are worst for patients with pre-existing susceptibility for cardiovascular disease and with increasing doses. Gastrointestinal complications like decreased mucin production, and less bicarbonate secretion due to inhibition of gastroprotective agents such as PGE2 and other prostaglandins are the other side effects of frequent DS administration. Similarly, in renal complications, decreased prostaglandin synthesis decreases renal perfusion and causes acute kidney injuries. In addition, diclofenac sodium causes hepatic complication and increases the liver transaminase level therefore, prolonged exposures of DS lead to hepatitis and cause life threating adverse effects. Therefore, controlled-release formulations of DS will be beneficial to overcome these adverse effects.[8-11]

Isabgol husk or psyllium husk is a natural water-soluble polymer obtained from dried ripe seeds *of Plantago ovata* plant that belongs to Plantaginaceae family. These seeds are rich in hydrophilic fibrous mucilage. Isabgol husk is widely used as traditional medicine in diseases including constipation, diabetes mellitus, ulcers, hypercholesterolemia etc. It has gained attention in pharmaceutical drug delivery system for development of hydrophilic matrix and encapsulating microparticulate due to its swelling and gelling mass properties.[12] An attempt has been made to crosslink the husk with various synthetic polymers. Singh B. *et al.*[13] modified husk with methacrylamide via $_{60}$Co gamma radiation crosslinked polymerization for formulation of sustained release rifampicin hydrogel.[13]

Polyvinyl alcohol PVA is a hydrophilic polymer which is widely used in formulation development due to its flexible processability, pH and temperature stability, non-toxicity, and biocompatibility.[14]

IPN microspheres made of natural hydrophilic polymers is a novel drug delivery approach for sustaining drug release in order to improve therapeutic efficacy and to reduce adverse effects.

This study aimed to sustain the release of Diclofenac sodium by formulating IPN microspheres by emulsion cross-linking method using Isabgol husk mucilage and PVA. [15]

MATERIALS AND METHODS

Materials

Diclofenac Sodium was a gift sample from Akums Pharma Pvt., Ltd., Haridwar, Uttarakhand, India. Isabgol was purchased from Sarvoday Sat Isabgol Factory, Siddhpur, Gujarat, India. All other chemicals and reagents were of the analytical grade and were used without further modifications.

Methods

Preformulation Study

Solubility

The maximum concentration of solute that can be dissolve in solvent at definite temperature is known as solubility. The solubility of drug was determined in a qualitative manner in distilled water, ethanol, methanol, and other organic solvent.[14]

Fourier Transform Infrared (FT-IR) spectroscopy

The identification of drug and drug-excipient compatibility was determined using FTIR spectroscopy. The FTIR evaluation was performed in scanning range of 4000-650 cm^{-1} for the characteristic peaks.[15]

Formulation of IPN microspheres using emulsion crosslinking method

An emulsion crosslinking method was used to produce interpenetrating polymer network-microspheres containing diclofenac sodium as given in Table 1. Poly Vinyl Alcohol (PVA) was first dissolved in hot boiling water above 80°C and the solution was cooled to ambient temperature. Isabgol husk mucilage was dissolved in 20mL of 2% sulfuric acid. The Isabgol mixture was added into the PVA solution with continuous stirring to get homogenous solution. Diclofenac sodium was dissolved in the 1mL ethanol and added to the mixture of Isabgol husk and PVA under continuous stirring to get a uniformed suspension. The suspension was added dropwise into the mixture of castor oil and span 80 (1%w/w), at a specific temperature as given in Table 1 and mixed for 30 min with continuous stirring at 1600 rpm. DL-glyceraldehyde was added in the suspension and the suspension was stirred for next 3-4 hr to get uniform microspheres. The prepared microspheres were filtered by Whatman filter paper and rinsed with acetone and n-Hexane to remove the oil and surfactant. The microsphere was allowed to dry for 24 hr at 50°C.[16,17] Total eight formulations was formulated to detect the effects of different formulations on the features of IPN microspheres as shown in Table 1.

Table 1: Formulation ratio and different variables used for preparation of IPN microspheres.

Formulations	F1	F2	F3	F4	F5	F6	F7	F8
Diclofenac sodium (mg)	200	200	400	400	400	`400	400	400
Isabgol husk Mucilage (gm)	1	1	1	1.6	1.6	1.6	1.6	1
Poly vinyl alcohol (in ml)	15	10	15	15	15	15	15	15
DL glyceraldehyde	2% 3mL	2% 3mL	2% 3mL	2% 3mL	2% 6mL	5% 3mL	3% 3mL	2%3mL
Castor oil (in ml)	100	100	100	100	100	100	100	100
Span 80 (in ml)	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Temperature (C)	70	70	60	60	60	70	60	70
Curing time (in hours)	3	3	4	4	4	4	4	4

EVALUATION OF PREPARED IPN MICROSPHERES

Percentage Yield

Percentage yield of all formulations was determined using the given formula.[16,17]

Percentage yield = [Practical weight (microsphere)/ Theoretical weight (drug and polymer)] x 100

Drug Entrapment Efficacy

Accurately weighed microspheres equivalent to 10 mg drug were dissolved in 50 methanol and sonicated for 10 min. The solution was filtered through Whatman filter paper and drug content were analysed using UV-vis spectrophotometer at 276 nm wavelength. The perecentage entrapment efficacy was determined by following formula.[16,17]

Percentage drug entrapped = [Practical drug content/ Theoretical drug content] x 100

Swelling Index

Swelling index is measured by placing 10 mg microspheres in 100 mL phosphate buffer (pH7.4) and 100 mL 0.1 N HCl (pH1.2) in separate container and allowed to swell for 24 hr at 37°C. Swelled microspheres were filtered and weighed. Swelling index was determined using following formula.[2,16]

Swelling Index = [(We - Wo) / Wo] x 100

Where, We= Weight of swelled microspheres.

Wo= Weight of dry microspheres.

Surface topographical study of the microsphere

Trinocular microscopy

The surface morphology of freshly manufactured microspheres after drying were obtained using an electron microscope (Olympus microscope).[18]

Scanning Electron Microscopy (SEM)

It is a technique for examining objects using electrons. SEM was conducted for shape and surface morphology of diclofenac sodium IPN microspheres. The microsphere sample was placed on the stubs using double sided adhesive tapes before being coated with a thin layer of gold (3-5 nm) for 75 sec at 40 W in a vacuum to make it electrically conductive. The images were captured at a magnification of 45X, 100X, 500X, and 1000X with a 20kv excitation voltage.[15,18]

Powder X-ray Diffractometry

The XRD patterns of diclofenac sodium, physical mixture of drug and polymer and drug loaded formulation were recorded using X-ray diffractometer (EXPERT-PRO). Samples were analyzed in Cu Kα radiation with voltage of 40kv and a current of 40mA in 5-30° range on the 2θ scale.[19]

In vitro drug release study

The drug release of DS from IPN microsphere was determined using USP paddle type (type II) dissolution apparatus (LABINDIA DS-8000) at 37°C±2°C. The dissolution study of drug is conducted in two media. Firstly in 0.1 N HCl (pH 1.2) for initial 2 hr and then in phosphate buffer (pH7.4) for 10 hr. At pre-determined time intervals of 1 hr, 5 mL aliquots were withdrawn, filtered through 0.45 membrane filter and replaced with equal volume of pre-warmed fresh medium to maintain sink condition. Following appropriate dilution, sample solution was analyzed for drug DS concentration by UV-spectrophotometry at 276 nm.[20,21]

IPN Microspheres Release Kinetics study

DD Solver was used to analyses the kinetics of drug release for the optimized formulations. The data of drug release study was fitted into different kinetic models like zero order, first order, Higuchi model, Korsmeyer-Peppas model and Hixon-Crowell model. The model having highest Model Selection Criteria (MSC) value, least Sum of Square Residual (SSR) and highest R^2 value were selected for describing the drug release mechanisms.[21-23]

Similarity factor (f2) study

In vitro drug release profile of the marketed Diclofenac sodium Sustained Release (SR) tablets, was performed under similar condition as done for *in vitro* drug release studies for test formulation for the release of Diclofenac sodium. The similarity factor between the both formulations was determined using the data obtained from the drug release studies. The similarity factor was analyses by DD solver software.[20,22,23]

RESULTS AND DISCUSSION

Solubility

Diclofenac sodium was found to be freely soluble in ethanol and methanol. DS was found to be sparingly soluble in water.

Fourier transform infrared spectroscopy

To identify the drug and polymers and to evaluate the drug-polymer compatibility, FTIR-spectroscopy was used. The FT-IR spectrum of Diclofenac sodium, physical mixture of drug polymer and optimized formulations (F6) was recorded and shown in Figure 1. The FT-IR spectrum of pure drug i.e., diclofenac sodium showed a characteristics peaks at 3387;93.937cm-^{1} due to -NH stretching of secondary amine. The absorption bands at 1320:95:282 cm-^{1} and 1249:95:428 cm-^{1} resulted from C-N stretching and the peaks at 1577:69.050 cm-^{1} and 1503:80:039 cm-^{1} due to C=O stretching and C=C stretching of carboxyl group respectively. [1] The C-C l stretching peak was observed at 750:62.218 cm-^{1}.

The FTIR-spectrum of physical mixture of drug-polymer showed absence of any interaction between the drug and polymer. The FTIR-spectrum microspheres (F6) showed all the principle characteristics peaks confirming the presence of diclofenac sodium in the formulations and no possibility of interaction between drug formulations excipients.[17,19]

X-ray Diffractometry

The X-ray diffractometry of pure drug (Diclofenac sodium), physical mixture of drug-polymer, and drug loaded formulation (F6) is shown in Figure 2. The diffraction pattern of pure diclofenac sodium showed high intensity crystalline peak at an angle of 13.40 with other minor peaks at 4.40 and 4.59. The findings showed that while the crystalline peaks of the drug and formulation are essentially identical, the peak strength of the formulation diffractogram decreases as a result of drug dilution with polymer.[24]

Evaluation of different parameter related to formulation

Percentage Yield

The percentage yield of all formulations was determined and results are shown in Table 2. The percentage yield ranged from 66.33% to 95.87%.

Entrapment Efficacy

The amount of diclofenac sodium entrapped in the microspheres showed dependency on the ratio polymers and cross linker used as shown in Table 2. It was found that an increase in the ratio increases drug entrapment efficay.

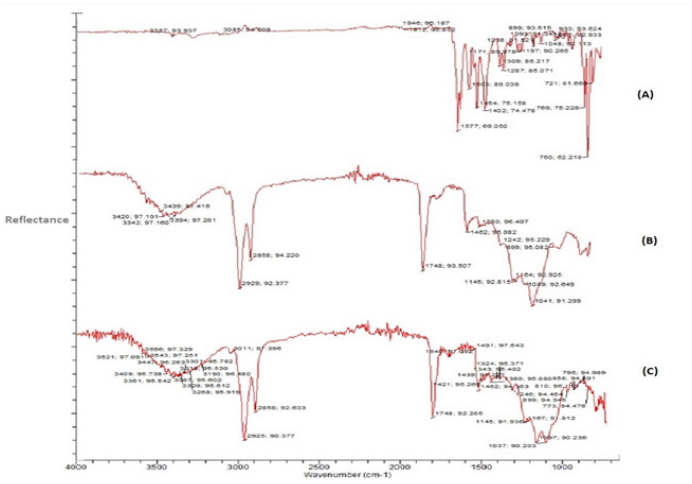

Figure 1: FTIR Spectrum (A) Diclofenac sodium, (B) Physical mixture of Diclofenac sodium and Isabgol husk mucilage (C) Microsphere formulation (F6).

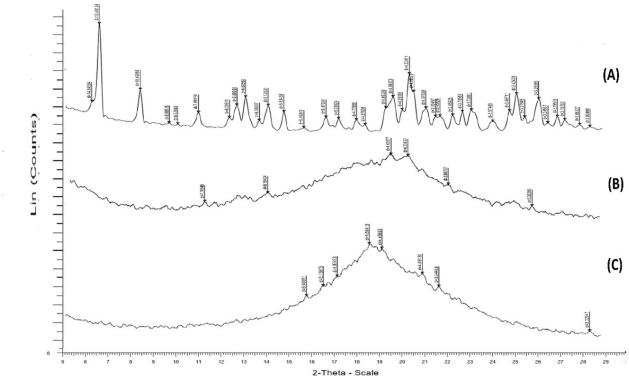

Figure 2: X-ray powder diffraction of (A) pure Drug Diclofenac sodium, (B) Diclofenac sodium and Isabgol husk mixture (C) formulations F6.

Table 2: Percentage Yield, Drug Entrapment Efficacy and swelling Index value.

Formulation	% Yield	% Entrapment Efficacy	Swelling Index After 24 hr. (%)	
			0.1 N HCl	Phosphate buffer 7.4
F1	93.61	48.12	60.12	78.54
F2	66.33	49.01	53.34	64.89
F3	93.37	57.38	62.52	79.56
F4	92.47	58.02	58.74	76.62
F5	91.35	49.11	52.64	69.82
F6	95.87	68.12	70.21	87.85
F7	87.19	62.11	64.52	80.56
F8	90.01	40.24	57.34	68.85

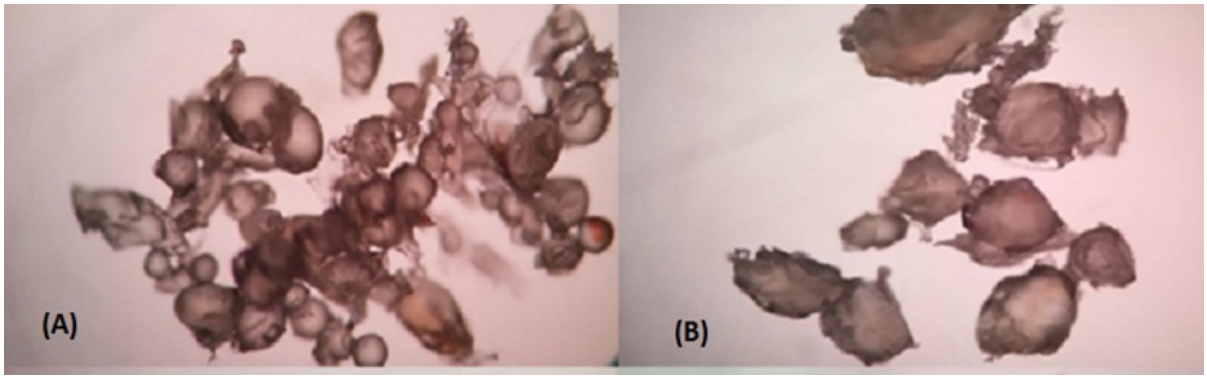

Figure 3: Images of (A) formulation F6 at 10x magnification and (B) Formulation F7at 10x magnification.

Swelling Index

The swelling study of different formulations was carried out in two different medium 0.1N HCl (pH 1.2) and phosphate buffer (pH 7.4) and the results were given in Table 2. The results showed that an incraese in the concentration of cross-linkers in IPN matrix, increases the percentage water uptake into matrix. This may be due to higher cross linking of polymers matrix that increased the density and porosity volume of polymeric network.

Surface Topological Study of Microspheres

Trinocular Microscopy

The surface topological study was conducted by the light microscope. The trinocular micrographs have been shown in Figure 3. The microspheres of different formulation were visualized under optical light 10X magnification. The microspheres were observed as nearly spherical shape.

Scanning electron microscopy

The SEM of prepared microspheres is depicted in Figure 4. The spherical IPN microsphere formed was quite large, according to the SEM analysis. The surface of the microsphere's formulation (F4) prepared at 60°C was irregular having micro droplets adhering to its surface. It indicates combining of fine droplets congealing and forming microspheres as shown Figure 4(B). The surface of the microspheres of (F6) prepared at 70°C was smooth, regular, and spherical as shown in Figure 4(A). The rate of water removal from the surface is high at high temperature that congealed husk hydrogel droplets into microspheres. The activation energy of the hydrogelation of Isabgol husk may be related to the smooth surface production of microspheres prepared at higher temperature as compared to low temperatures. In compared to lower temperatures, the accomplishment of activation energy may occur more quickly at higher temperatures, leading to spherical microspheres.

Cai *et al.*,[18] research studies findings state that drug release by pore diffusion process is also influence by internal and external porosity of the microspheres. In Figure 4(C) and 4(D) parts of SEM images depicted the presence of pores on the surface morphology of microspheres which enhances the drug release.[18]

In vitro Drug Release Study

In vitro drug release studies of IPN microspheres of Diclofenac sodium was measured in 0.1 N HCl pH1.2 and phosphate buffer pH7.4. Diclofenac sodium has pKa value of 4, and it is practically insoluble in acidic medium, therefore there is slight release of drug (≤10%) in acidic pH. DS release from prepared

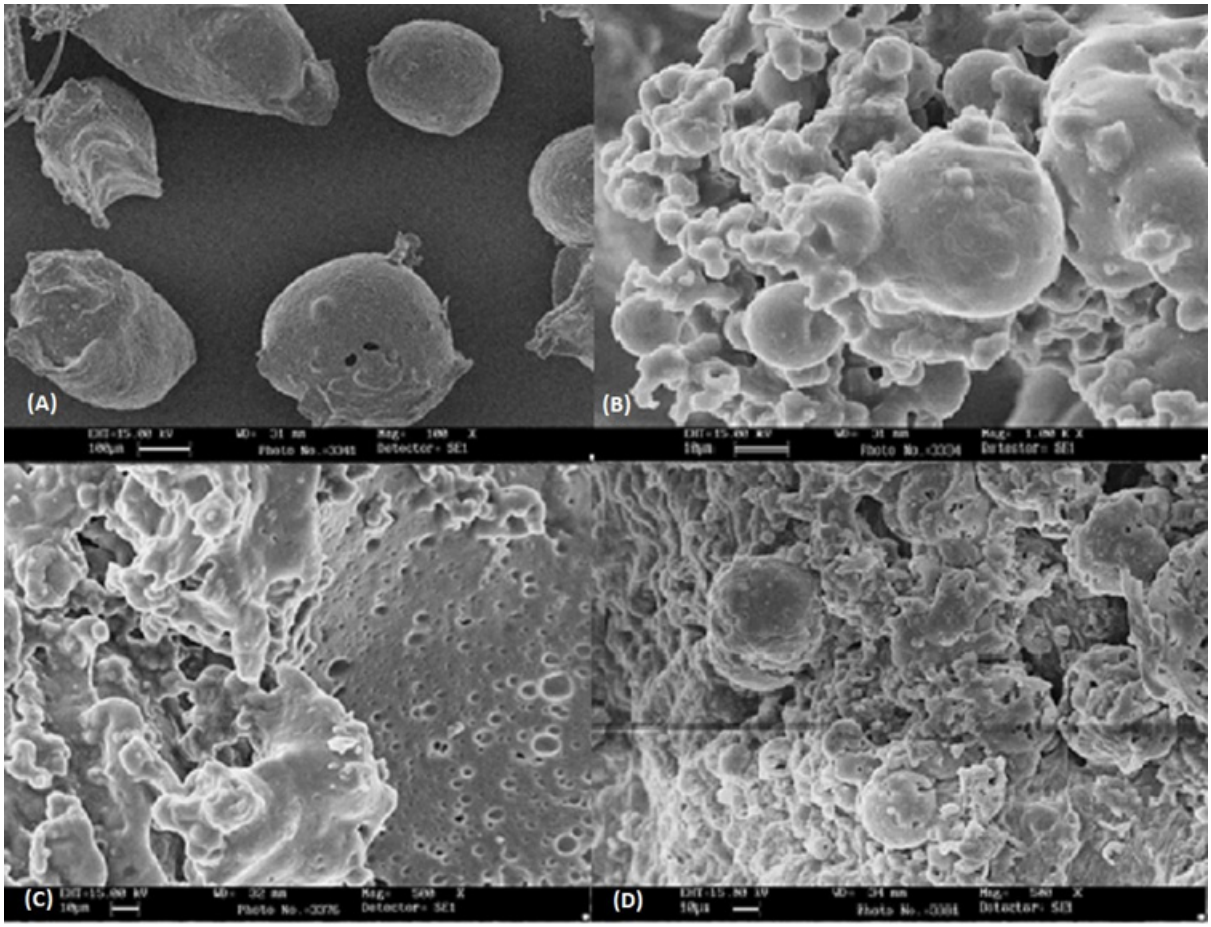

Figure 4: SEM of (A) formulation F6 Temp 70°C (B) formulation F4 Temp. 60°C. (C) Surface view of Formulation F4 (D) Surface view of Formulation F6.

Table 3: Optimized formulation *in vitro* drug release model.

Fitting Release	R^2	R^2 adjusted	SSR	MSC
Zero-order	0.9791	0.9791	161.9904	3.4964
First-order	0.9229	0.9229	596.8994	2.1922
Higuchi	0.8374	0.8374	1258.9497	1.4459
Korsmeyer-Peppas	0.9912	0.9912	78.9773	4.1187
Hixon-Cornwell	0.9442	0.9442	432.1109	2.515

microspheres were studied in acidic buffer pH1.2 for initial 2 hr and then in phosphate buffer pH7.4 for a period of 10 hr.

At acidic medium, microspheres shrink to tighting of the gel network, resulting in low drug release from IPN microspheres. In alkaline pH the drug was released in the controlled manner by diffusion and slow erosion of IPN matrix. The *in vitro* release data showed that the release of drugs in acidic medium is very low (<10%) and the release was subsequently increased at higher pH value. The maximum release of drug was 94.12% from the formulation F6 after 10 hr as shown in Figure 5.

Release kinetics of IPN microsphere using kinetic models

The kinetic of drug release of optimized formulations (F6) was performed using DD Solver. The correlation coefficient (R^2) and the sum of square residuals (SSR) value of each model was calculated and given in Table 3. The optimized formulation followed Korsmeyer-Peppas model, because this model has the lowest SSR value and highest R^2 valuae equal to 78.9773 and 0.9912 respectively and adjusted R^2 equal to 0.9912. Among all the model evaluated the Model selection criteria (MSC) found to be highest (4.1187) for Korsmeyer-Peppas model, indicating that the characteristics of drug release are best described by this model.

Table 4: Similarity factor results.

Time	% Drug release of Reference	% Drug release of optimized formulation (F6)	F2
0.5	9.62	5.54	68.83
1	16.31	15.52	86.41
2	22.05	19.23	76.21
3	28.11	26.23	77.79
4	35.12	32.32	76.34
5	44.21	39.45	65.65
6	56.07	53.81	65.57
7	68.56	66.76	68.48
8	88.18	85.52	77.32
9	98.23	94.31	69.65

Average value of f2 = 75.92.

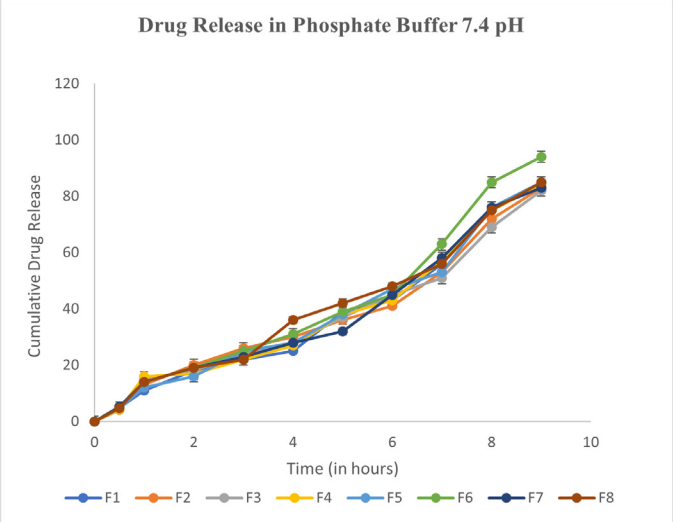

Figure 5: Drug Release Graph of formulation in Phosphate buffer pH(7.4).

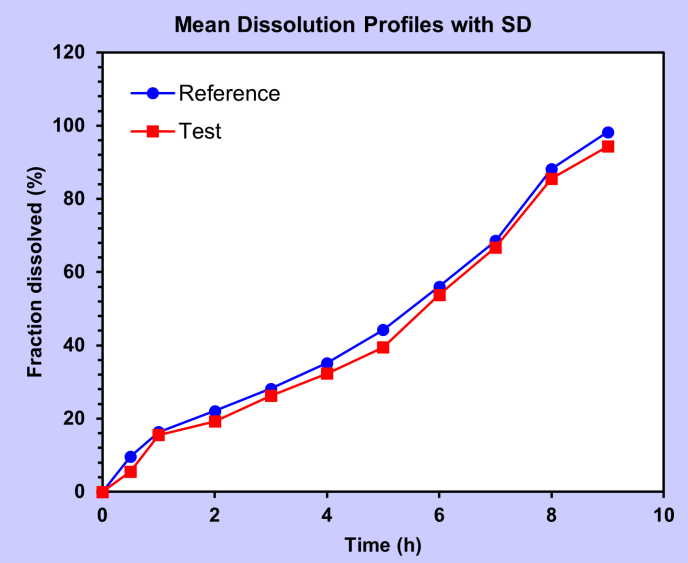

Figure 6: Similarity factor (f2) between optimized test formulation (F6) and reference formulation (Voveran SR tablet).

The release exponent value (n) of 0.687 indicate non-Fickian diffusion of Diclofenac Sodium from IPN microspheres.

Similarity Factor

The purpose of dissolution testing is to ensure the uniformity of product from batch to batch, to predict the bioavailability for formulation and development and when changes are made to an existing formulation. The similarity factor (f2) used to compare the two dissolution profiles of test and reference products. The similarity factor between the optimized formulation (F6) and marketed Voveran SR tablet of diclofenac sodium was calculated using DD solver. The release of DS showed the similarity factor (f2=75.92) greater than 50 as shown in Table 4.

It was confirmed from Figure 6 that the release of DS from optimized formulations were similar to that of the marketed formulations.

CONCLUSION

In this study, IPN microspheres of Diclofenac sodium was prepared using Isabgol husk and PVA. This study disclosed that hydrophilic group of Isabgol husk can be cross-linked efficiently and can be modified into spherical microporous matrix system. This study also showed that the surface topology of microspheres was affected by ratio of cross-linking agent used and temperature during the process. The cross-linked Isabgol husk showed sustained release behavior to encapsulated Diclofenac sodium. The drug release was regulated by swelling and penetration of dissolution media into microspheres. The article suggested that

DS IPN microspheres are promising pharmaceutical dosage form for providing controlled drug release and avoiding dose related side effects.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

IPN: Inter-penetrating network; **FTIR:** Fourier Transform infrared; **XRD:** X-ray diffraction; **PVA:** Poly vinyl alcohol; **SEM:** Scanning Electron Microscopy.

SUMMARY

Diclofenac sodium is a Non-Steroidal Anti-Inflammatory Drug (NSAID). The drug has a short half-life of 1.2-2 hr therefore, frequent administration of DS is required which results in dose related side effects. In this work IPN microspheres were prepared using Isabgol Husk and PVA by emulsion crosslinking method. The optimized microspheres (F6) were spherical in shape with 68.12% drug encapsulation. The *in vitro* drug release study showed sustained drug release for more than 10 hr. The *in vitro* drug release data were fitted in various kinetic model to understand the mechanism of drug release from microspheres using DD solver. The characteristics of drug release were best described by Korsmeyer-Peppas model. The release of DS showed the similarity factor (f2) factor (f2=75.92) greater than 50. It is therefore confirmed that the release of DS from optimized formulations were similar to that of the marketed formulations (Voveran SR tablet) of diclofenac sodium.

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