eISSN: 2321–323X
pISSN: 2395-0781

Innovations in Pharmaceuticals and Pharmacotherapy

www.innpharmacotherapy.com

Review article

Development and evaluation of oxiconazole nitrate hydrogel as a topical drug delivery system

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Abstract

Background: The Hydrogels are hydrophilic, three-dimensional networks, which are able to imbibe large amounts of water or biological and thus resemble, to a large extent, a biological tissue. They are insoluble due to the presence of chemical and/or physical crosslinks such as entanglements and crystallites. These materials can be synthesized to respond to a number of physiological stimuli present in the body, such as pH, ionic strength and temperature. **Aim:** The aim of this research article was to present a concise review on the applications of hydrogels in the pharmaceutical hydrogel characterization and analysis of drug release from such devices. **Method:** In the present study, an attempt has been made to formulate the topical drug delivery system of Oxiconazole Nitrate in the form of Hydrogel. There are 18 Batches were used for the formulation process. **Result:** The IR shows that there is no interference in the drug and polymer at the molecular level. The Encapsulation efficiency of different hydrogel was estimated range of 95-98.5% which indicates uniform distribution of the drug throughout the hydrogel. The percentage drug releases of F1 to F18 batches are 23.40% to 80%. Spreadability in range of 22.20-27.23g.cm/sec, and formulation were easily extrudable from the tube. It was found that pH of all the formulation is in the range of 6.21to 6.46 that suits the skin pH indicating skin compatibility. **Conclusion:** The formulation can be estimated that it was a good topical formulation and technique use for the future aspect.

Keywords: Carbopol, Chitosan, Hydrogel, Oxiconazole nitrate, Tamarinds.

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1. Introduction

Topical delivery can be defined as the application of a drug containing formulation to the skin to directly treat cutaneous disorders (e.g. acne) or the cutaneous manifestations of a with the intent of containing the pharmacological or other effect of the drug to the surface of the skin or within the skin [1].

Topical gels are transparent or translucent semisolid formulations containing a high ratio of solvent/gelling agent. Semi-solid formulation in all their diversity dominates the system for topical delivery [2]. Topical application of drugs offers potential advantages of delivering the drug directly to the site of action and acting for an extend period of time [3].
Skin is one of the most extensive and readily accessible organs on human body for topical administration and main route of topical drug delivery [4-6].

Hydrogel

Hydrophilic gels called hydrogels are cross-linked materials absorbing large quantities of water without dissolving. Softness, smartness, and the capacity to store water make hydrogels unique materials. The ability of hydrogels to absorb water arises from hydrophilic functional groups attached to the polymer backbone while their resistance to dissolution arises from cross-links between network chains. Water inside the hydrogel allows free diffusion of some solute molecules, while the polymer serves as a matrix to hold water together [7].
Another aspect of hydrogels is that the gel is a single polymer molecule, that is, the network chains in the gel are connected to each other to form one big molecule on macroscopic scale. It is natural to expect that the conformational transitions of the elastically active network chains become visible on the macroscopic scale of hydrogel samples.
The gel is a state that is neither completely liquid nor completely solid. These half liquid-like and half solid-like

properties cause many interesting relaxation behaviors that are not found in either a pure solid or a pure liquid. From the point of view of their mechanical properties, the hydrogels are characterized by an elastic modulus which exhibits a pronounced plateau extending to times at least of the order of seconds, and by a viscous modulus which is considerably smaller than the elastic modulus in the plateau region [8, 9].

Oxiconazole nitrate is an imidazole derivative whose antifungal activity is derived primarily from the inhibition of ergosterol biosynthesis, which is critical for cellular membrane integrity. It has in vitro activity against a wide range of pathogenic fungi. Chemically, oxiconazole nitrate is 2', 4'-dichloro-2-imidazol-1-ylacetophenone (Z)-[0-(2, 4-dichlorobenzyl) oxime], mononitrate [10, 11].

Carbopol-934 is a polyacrylic acid polymer which may be used as bioadhesive vehicles for drug delivery. In order to have a greater understanding of the factors affecting drug release from these gels, it is necessary to develop methods of studying their physical properties [12].

Chitosan is the most abundant natural amino polysaccharide and is estimated to be produced annually almost as much as cellulose. It has become of great interest not only as an underutilized resource, but also as a new functional material of high potential in various field [13].

Tamarindus indica is a plant that is used in traditional medicine for the treatment of cold, fever, stomach disorder, diarrhea and jaundice and as skin cleanser. To evaluate the scientific basis for the use of the plant, the antimicrobial activities of extracts of the stem bark and leaves were evaluated against some common gram negative and gram positive bacteria and fungi [14, 15].

In this research work to present a concise review on the applications of hydrogels in the pharmaceutical hydrogel characterization and analysis of drug release from such devices. In the present study, an attempt has been made to formulate the topical drug delivery system of Oxiconazole Nitrate in the form of Hydrogel.

2. Materials and Methods

Materials

Chitosan was gifted from Mytsa Fisheri Technology Cochin. Oxiconazole nitrate purchased from Yarrow Chem Pharmaceutical, Mumbai, India. Carbopol-934 was purchased from Zim Lab Nagpur. Tamarind seeds powder purchased from local market. All the other reagents were analytical grade.

Preparation of Chitosan Derivative

Weighed 5 gm of chitosan added in 100ml of 2% glacial acetic acid to formed slurry of chitosan. Slurry of chitosan stirred with Magnetic stirrer with speed 1000 rpm for continue 2 hours (Remi electrotechnik limited, Thane, India). Then 100ml of 0.1M tri-sodium citrate was added into the slurry chitosan and continued stirred for 4 hours. This formulated slurry or suspension was further proceeded sonicate for 10min. Then centrifuge at 500rpm for 10min. After completion of centrifugation collect the sediment part. Dry acetone (60 ml) was added into separated sediments. Sediment part filtered and dried at 48 ^{0}C for 12hr. and stored in a well closed container [16, 17].

Isolation of *Tamarindus indica* seeds powder

Tamarindus indica seeds were dried in sun light or preferably in oven at 105 ^{0}C. Before isolating the powder care was taken when drying the final isolated/extracted powder. It must be dried at a very in a vacuum. The dried material was crushed into fine powder.

200g of tamarind seeds were soaked in double distilled water and boiled for 5 hours to remove the outer dark layer. To inner white portion sufficient amount of doubled distilled water was added and boiled under stirring condition in a water bath to remove outer layer then crushed into fine powder [18].

Preparation of Oxiconazole Nitrate Hydrogel

There are 18 batches were used for the preparation of Hydrogel. Above mentioned chitosan derivatives, isolation of Tamarindus indica, HPMC E5, HPMC E15, Eudragite L-100. Carbopol-940, Carbopol-971, Carbopol-974, Carbopol-934 and using oxiconazole nitrate drug were used for the preparation of hydrogel [19, 20] Shown in Figure 1.

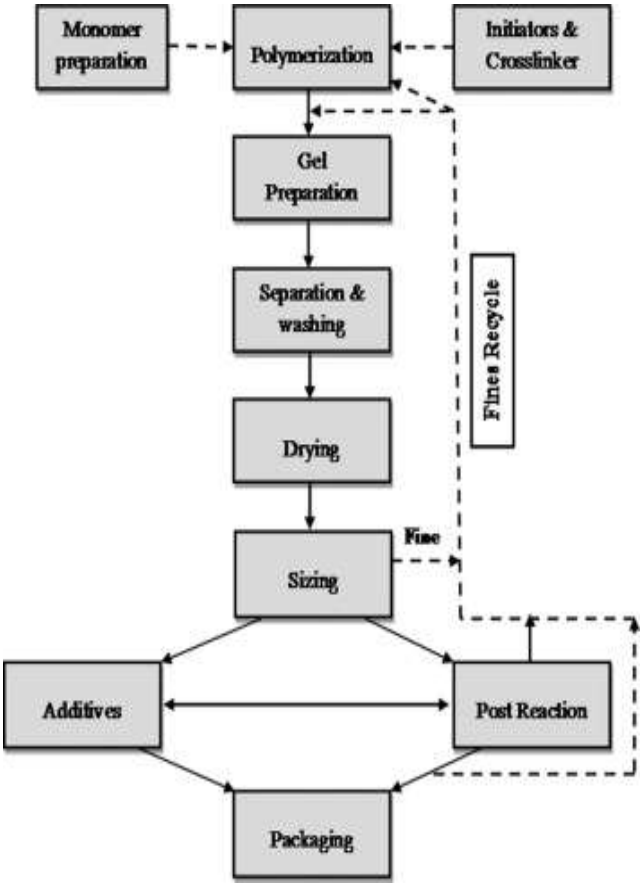

Figure 1: Preparation of Hydrogel.

Table No 1: Composition of Hydrogel of Oxiconazole Nitrate

Formulation Batches	Oxiconazole Nitrate (g)	Chitosan Derivatie (g)	Carbopol-934 (g)	Tamarind seed powder (g)	Methyl paraben (g)	Water (Up to) (g)
F1	0.5	3.0	3.0	-	0.5	100
F2	1.0	3.0	3.0	-	0.5	100
F3	1.5	3.0	3.0	-	0.5	100
F4	2.0	3.0	3.0	-	0.5	100
F5	2.5	3.0	3.0	-	0.5	100
F6	3.0	3.0	3.0	-	0.5	100
F7	0.5	-	3.0	3.0	0.5	100
F8	1.0	-	3.0	3.0	0.5	100
F9	1.5	-	3.0	3.0	0.5	100
F10	2.0	-	3.0	3.0	0.5	100
F11	2.5	-	3.0	3.0	0.5	100
F12	3.0	-	3.0	3.0	0.5	100
F13	0.5	3.0	-	3.0	0.5	100
F14	1.0	3.0	-	3.0	0.5	100
F15	1.5	3.0	-	3.0	0.5	100
F16	2.0	3.0	-	3.0	0.5	100
F17	2.5	3.0	-	3.0	0.5	100
F18	3.0	3.0	-	3.0	0.5	100

Pre-formulation study

The oxiconazole nitrate pre-formulation study using organoleptic, appearance, and physical properties.

Characterization of oxiconazole Nitrate Hydrogel Encapsulation efficiency (% EE)

The oxiconazole nitrate encapsulated was determined by UV–vis spectrophotometer (HITACHI U-2900, Tokyo, Japan). 10 mg of hydrogel were dispersed in ethanol (2 ml), stirred for proper dissolution and extracted in phosphate buffer solution (pH 7.4). Stirring was continued for 30 min at room temperature to evaporate organic solvent completely. Then the solution was filtered, the residue was washed with phosphate buffer solution and drug content was determined in the filtrate after appropriate dilution with a phosphate buffer solution at 210 nm using UV-vis spectrophotometer. The EE was expressed as the percentage of drug incorporated in the formulation relative to the total amount of drug (theoretical quantity) used in the formulation. The EE of oxiconazole nitrate was calculated using the following equation 1.

$$\text{Drug entrapment efficiency} = \frac{\text{actual drug content}}{\text{theoretical drug content}} \times 100$$

Fourier Transform Infrared (FTIR) spectroscopy study

The chemical structure of the pure Oxiconazole Nitrate, polymers and drug loaded Hydrogel were analysed using FTIR spectrophotometer (FTIR-8400, Shimadzu, Asia Pacific Pvt. Ltd. Singapore) by KBr pellet method. Sample (1 mg) was mixed with KBr (40 mg) and formed into a disk by applying force in a manual press. Spectra were recorded in the scan range of 4000–500 cm−1.

In - vitro drug dissolution studies

Drug release from hydrogel was performed *in-vitro* using phosphate buffer (pH 6.8) for 10 hr. in Dissolution Test App. (Model FC 6X12R Electrolab TDT-08 L, India) USPXXVIII, type-I (100 RPM, 37 ± 0.5 ^{0}C). The dissolution medium of phosphate buffer (pH 7.4) was prepared according to Indian Pharmacopoeia 2007 [21]. The batch size in mg of hydrogel was taken for the drug released study. From 900 ml phosphate buffer (i.e. dissolution medium) in each jar containing micro-/nanospheres, 10 ml were withdrawn automatically at predetermined time intervals and replenished with 10 ml volume of fresh dissolution media to maintain the sink condition. The samples were filtered through a Whatman filter paper no. 41. The oxiconazole nitrate content of each sample was assayed by UV–Vis spectroscopy at λmax of 210 nm.

3. Result and discussion

Preformulation study

Table No 2: Physical characterization of Oxiconazole Nitrate

Experimental	Property Studied	Result
Organoleptic property	Color	White
	Odour	Odourless
	Taste	Slight bitter
	Nature	Hydrophilic
Identification of drug sample	Melting point	138^0C

Physical appearance

The prepared oxiconazole hydrogel were inspected visually for color, homogeneity, consistency. All formulations showed yellowish color, smooth appearance, formulation showed suitable homogeneity and consistency (Table 3).

Measurement of pH:

The pH of hydrogen formulations was in the range of 5.50 to 6.70 which considered acceptable to avoid the risk of skin irritation upon application to skin result are shown in Table 3 and Figure 2.

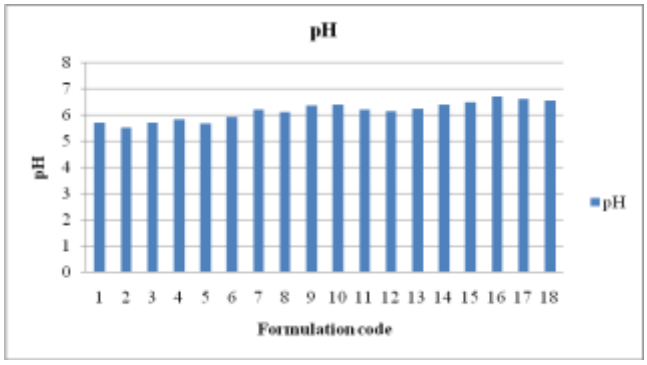

Figure 2: pH of hydrogel formulation (F1-F18)

Table No 3: Physical appearance, pH, Drug content, viscosity

Formulation	Color	Feel on application	pH
F1	Yellowish	Smooth	5.69
F2	Yellowish	Smooth	5.80
F3	Yellowish	Smooth	5.70
F4	Yellowish	Smooth	5.80
F5	Yellowish	Smooth	5.67
F6	Yellowish	Smooth	5.90
F7	Yellowish	Smooth	6.18
F8	Yellowish	Smooth	6.09
F9	Yellowish	Smooth	6.34
F10	Yellowish	Smooth	6.39
F11	Yellowish	Smooth	6.20
F12	Yellowish	Smooth	6.14
F13	Yellowish	Smooth	6.22
F14	Yellowish	Smooth	6.36
F15	Yellowish	Smooth	6.48
F16	Yellowish	Smooth	6.70
F17	Yellowish	Smooth	6.60
F18	Yellowish	Smooth	6.54

Characterization of Hydrogel

Encapsulation Efficiency (EE):

The EE are shown in Table 4 and Figure 3. The EE of different hydrogel was estimated and the results were in official limit if the range of 95-98.5 % which indicate uniform distribution of the drug throughout the hydrogel.

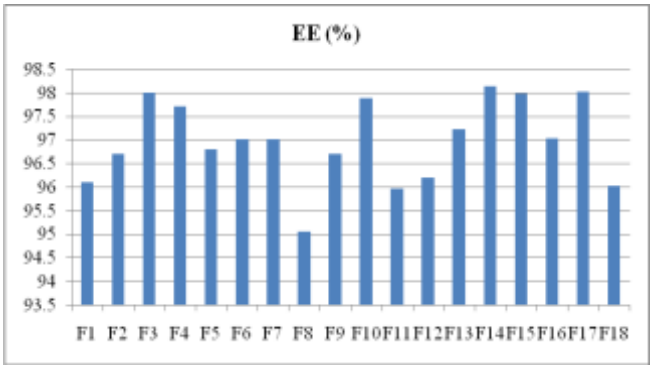

Figure 3: % Encapsulation efficiency

Table No 4: Spredability, Extrudability and % EE

Formulation code	Spreadability gm*cm\sec	Viscosity (cps)	EE (%)
F1	15	3120	96.09
F2	13	3120	96.70
Formulation code	Spreadability gm*cm\sec	Viscosity (cps)	EE (%)
F3	15	3120	98.0
F4	14	3120	97.70
F5	14	3120	96.80
F6	15	3120	97.0
F7	12	6240	97.01
F8	14	6240	95.05
F9	12	6240	96.70
F10	12	6240	97.88
F11	12	6240	95.96
F12	13	6240	96.20
F13	12	6340	97.22
F14	13	6340	98.13
F15	11	6340	97.98
F16	14	6340	97.02
F17	11	6340	98.01
F18	13	6340	96.01

Fourier transform infrared (FTIR) spectroscopy study

IR study was carried to check the compatibility between the selected excipients and Oxiconazole nitrate. The spectra obtained for IR studies at wavelength from 4000 cm-1 to 400 cm-1. In IR of Oxiconazole nitrate (Figure 4) the peak at 2960 cm-1 C-H stretching, at 1455 cm-1 C=N, at 1368 cm-1 N-O (of cis isomer), at 3119 cm-1 C-H (aromatic). In chitosan IR (Figure 5), at 1629 cm-1 C=O, at 1372 cm-1 C-H, at 3279 cm-1 OH bonding. In IR spectra of chitosan derivatives (Figure 6) shows; at 1571 cm-1 C=N, at 1646 cm-1 C=O, at 3281 cm-1 OH bonding, at 1571 cm-1 NH stretching. In spectra of Tamarind seeds powder (Figure 7) shows major peak at 3279 cm-1 OH bonding. After interpretation through the spectra it was confirmed that there were no major shifting as well as any loss of functional peaks between the spectra of pure oxiconazole nitrate, chitosan derivatives, tamarind powder, and physical mixture of drug and polymers agent. From the IR studies it was concluded that, the selected gelling agent are compatible with the selected drug Oxiconazole Nitrate. The entire peaks are near about the hydrogel formulation. Thus, indicating no existence of the chemical interaction between the oxiconazole nitrate and polymers (Figure 8).

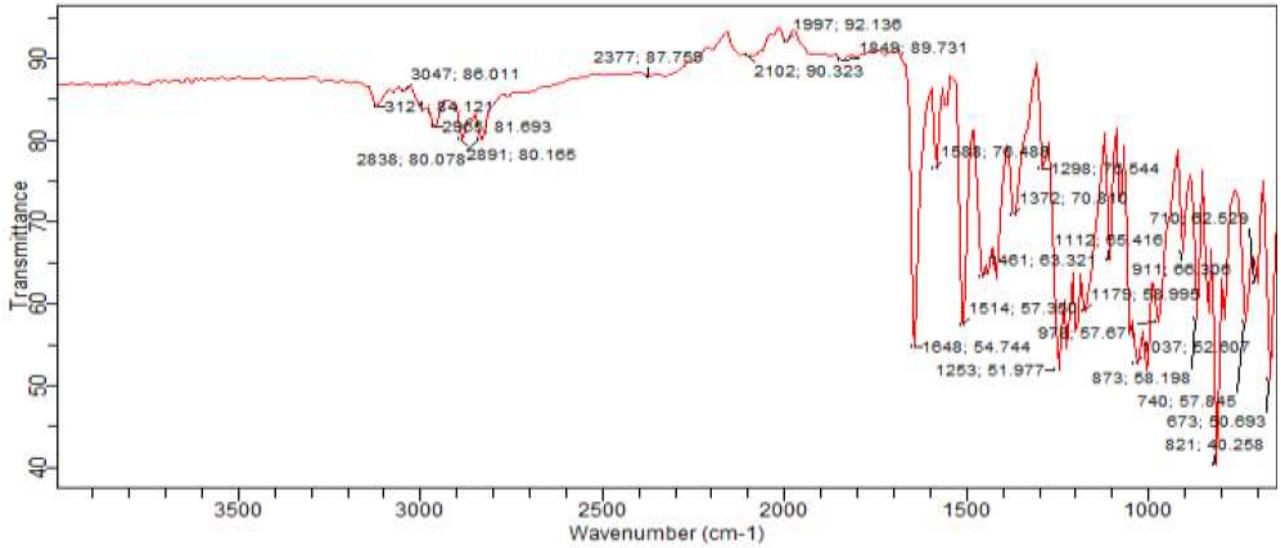

Figure 4: IR Spectrum of pure Oxiconazole Nitrate

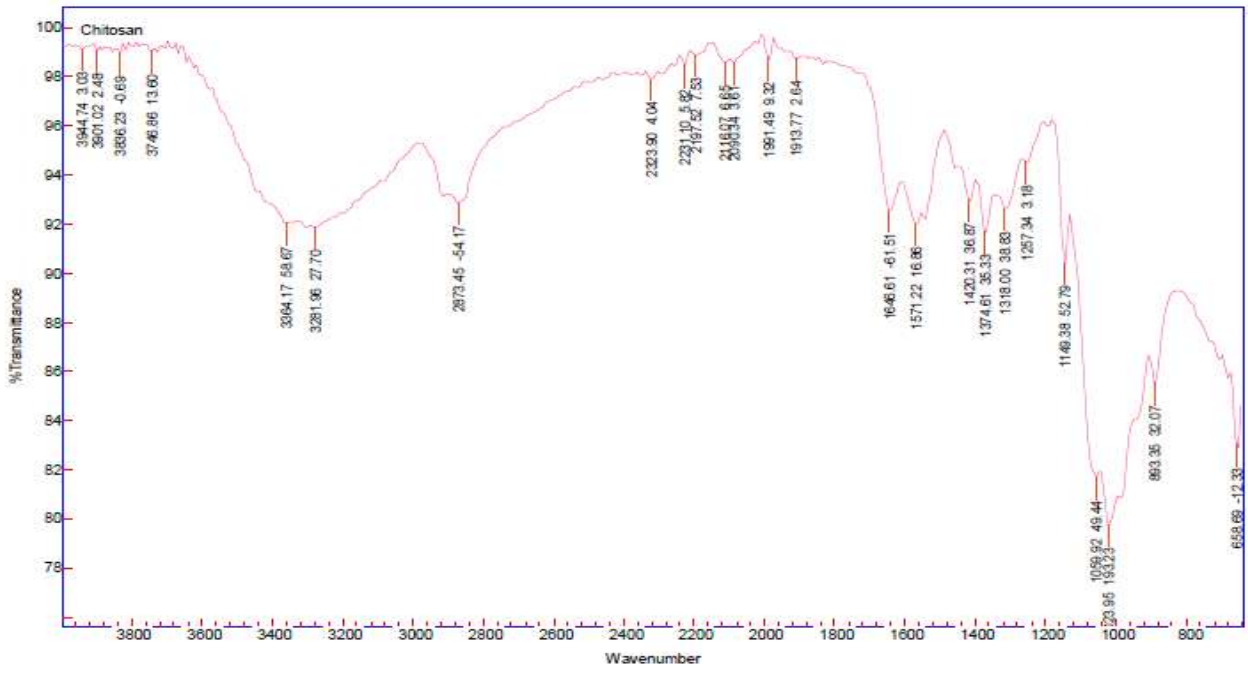

Figure 5: IR Spectrum of chitosan

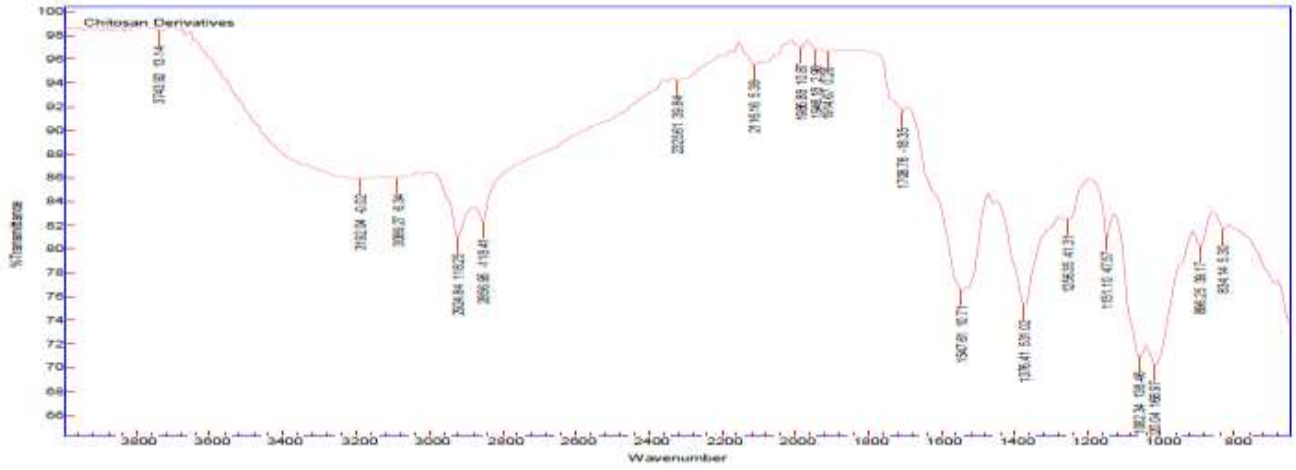

Figure 6: IR Spectrum of chitosan Derivative

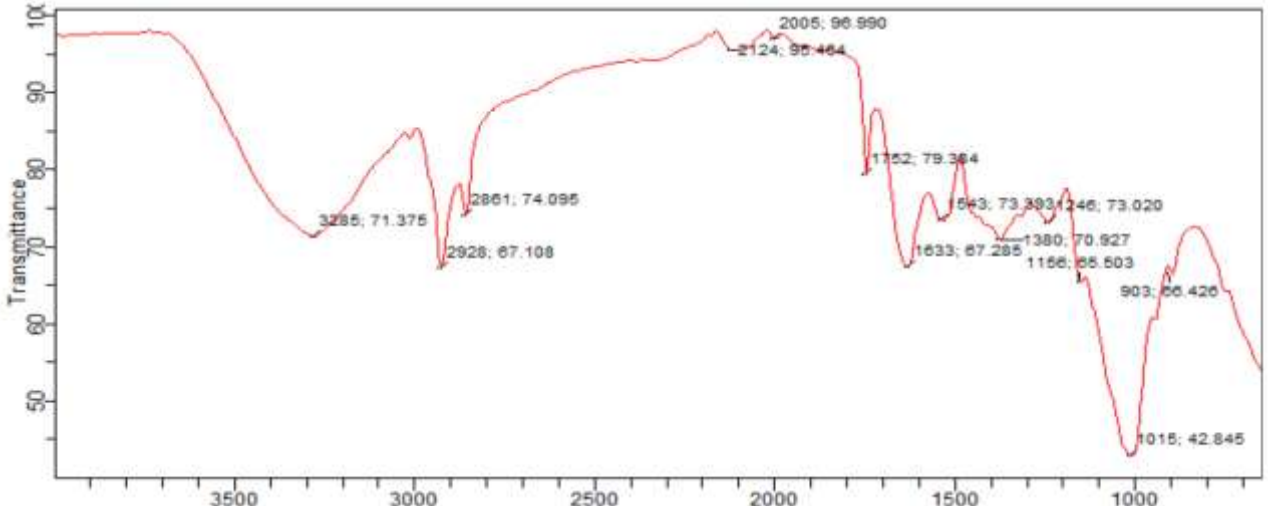

Figure 7: IR Spectrum of Tamarind seeds powder

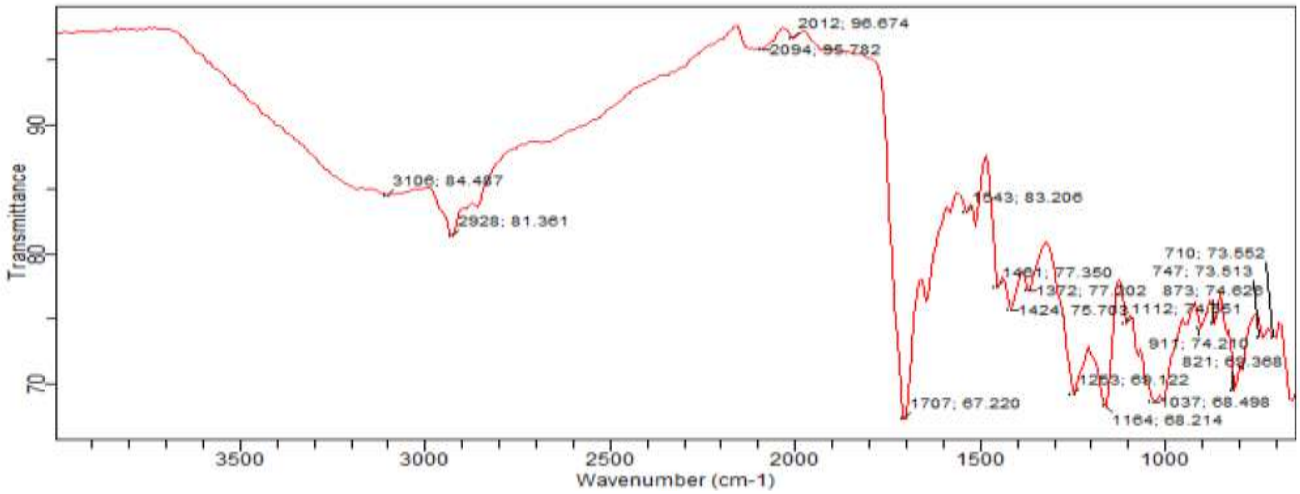

Figure 8: IR Spectra of drug and polymers mixture (Formulation).

In-vitro drug Release

In-vitro release of oxiconazole nitrate from different hydrogen formulations was carried out in phosphate buffer pH 7.4 for 10 hour at 37 ^{0}C was investigated and the results are represented in Figure 9-11. The plot of % drug release

Vs time were plotted % drug release from batches F1-F6 35%, 39.22%, 42.8%, 50%, 67.59% and 80% respectively. The plot of % drug release Vs time were plotted % drug release from batches F7-F12 23.4%, 29.5%, 30.48%, 38.8%, 40.85% and 57.62% respectively. The plot of % drug release Vs time were plotted % drug release from batches F13-F18 42.32%, 47.8%, 53.84%, 55%, 57.6% and 37.6% respectively. It was noticed that the release of oxyconazole nitrate from its hydrogel can be ranked in fallowing descending order F6>F5>F4>F3>F2>F1 and F12>F11>F10>F9>F8>F7 and F17>F16>F15>F14>F13>F18. From the above observation it was observe that concentration of drug increased, % drug release increase.

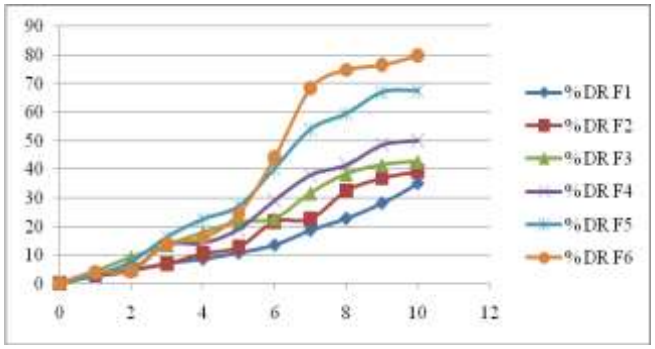

Figure 9: % drug release of F1-F6

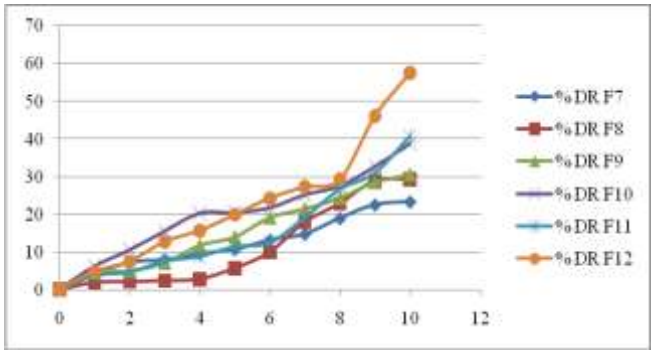

Figure 10: % drug release of F7-F12

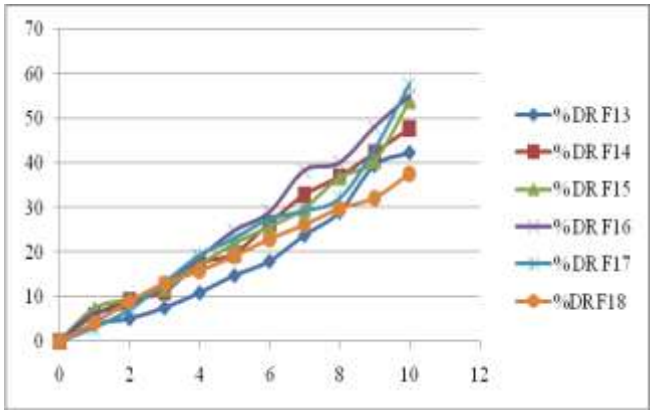

Figure 11: % drug release of F13-F18

Stability studies

The prepared oxiconazole nitrate hydrogel formulations were found to be stable after subjected to stability studies at 0^0C and 40^0c for period of 1 month. No significant change was noticed in the parameters evaluated for color, pH, Spreadability of formulation shown in Table 4.

Table No 5: Stability study of formulated hudrogel (after stability study)

Formulation Code	Color	pH	Spreadability
F2	Brownish	5.80	13
F8	Yellowish	6.09	14
F14	Yellowish	6.36	13

Conclusion

In the present study, an attempt has been made to formulate the topical drug delivery system of Oxiconazole Nitrate in the form of Hydrogel. Oxiconazole Nitrate is widely used antifungal agent mostly used for fungal disease. The sample Oxiconazole Nitrate was firstly characterized for its identification by using physical characterization test like melting point, UV absorption in phosphate buffer pH 7.4, FTIR. The results of these entire tests were found to be within the standard limit and in compliance with specification of BP. 2005. Hydrogels were developed using gelling agent Chitosan Derivative, carbopol 934 and tamarind seed powder as gelling agents, methyl paraben as a preservative and Oxiconazole Nitrate as hydrophobic drug in water soluble gel bases. All the formulation developed were evaluated for the post formulation studies like color, pH, viscosity, Spreadability, extrudability, drug content, *In-vitro* drug release and stability studies. And all the result observed was within official limit. Formulation developed using carbopol 934 show shiny white in color where as hydrogel developed using HPMC 2910 showed white in color. No phase separation was observed in formulation. Drug content was found in the range of 95.55-98.45 %mg, Spreadability in range of 22.20-27.23g.cm/sec, and formulation were easily extrudable from the tube. It was found that pH of all the formulation is in the range of 6.21to 6.46 that suits the skin pH indicating skin compatibility. This is the primary requirement for a good topical formulation.

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