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HYDROGEL BASED ON LEVOFLOXACIN AND PROBIOTICS WITH ANTIBACTERIAL PROPERTIES AGAINST *STAPHYLOCOCCUS AUREUS*: FORMULATION AND EVALUATION

Article History:

Name of Authors & Affiliation

[1]Nandini Sinhmar
Department of Biotechnology, Kurukshetra University, Kurukshetra, Haryana-136119
[2*]Bindu Battan
Department of Biotechnology, Kurukshetra University, Kurukshetra, Haryana-136119, India.
[3]Surender Verma
Department of Pharmaceutical Sciences, Kurukshetra University, Kurukshetra, Haryana-136119, India.
[4]Sulekha Chahal
Department of Biotechnology, Kurukshetra University, Kurukshetra, Haryana-136119, India.
[5]Jitender Sharma
Department of Biotechnology, Kurukshetra University, Kurukshetra, Haryana-136119, India.
[6]Rimpy
Department of Pharmaceutical Sciences, Kurukshetra University, Kurukshetra, Haryana-136119, India

Corresponding Author:
Bindu Battan, Department of Biotechnology, Kurukshetra University, Kurukshetra, Haryana-136119, India. *Email:* bbattan@kuk.ac.in

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***Abstract*:** Gels have become a viable, feasible, encouraging, and promising option for the topical delivery of drugs to the affected areas or sites. This new research enables a local, direct, and regulated release of the drug, with numerous benefits that have many advantages when compared with the oral delivery of drugs. The objective was to develop a dermatological gel with good therapeutic effects, improved dispersibility, and storage stability, suitable for local drug administration following topical application. Hydrogels are a novel antimicrobial formulation that can eliminate pathogenic microbes; therefore, they have been exploited in many pharmaceutical applications, including medications, sanitisers, as an effective vesicular drug delivery system, and as personal care products. Probiotics have been consumed to provide therapeutic effects for improving skin health in addition to gut health when applied topically. This research article is focused on presenting a preparation and evaluation of characteristics of probiotics-based hydrogels as a conventional therapeutic agent using different polymers, including HPMC, Sodium CMC, and Sodium alginate, together with preservatives. The antimicrobial activities of all the prepared hydrogels loaded with probiotics filtrates of *Lactiplantibacillus plantarum*, *Lactiplantibacillus pentosus* and *Bifidobacterium animalis* against *Staphylococcus aureus*, the most opportunistic pathogen responsible for skin diseases and maintain the skin health and microbiome.

***Keywords*:** Skin, Probiotics, Hydrogels, Levofloxacin, Pharmaceutical products.

INTRODUCTION

The skin is the largest organ of the human body, covering approximately an average area of 1.7 m^2. The skin has a highly effective self-renewal capacity and forms a barrier between the internal and external environments. Human skin is a perfect, unmatched organ that itself controls the cycle of water and heat gain and loss by regulating pH, humidity, and temperature. It also protects and defends the body against harmful microbes by secreting specific antimicrobial secretions, including proteases, sebum, antimicrobial peptides, and lysosomes.[1] Despite this, the skin's commensal microbiome creates a complex and intricate ecosystem and can prevent colonisation of harmful microbes by competing with them.[2] The skin, which makes up 10% of the total body, is a huge and accessible organ that has several sites or locations for the administration of therapeutic or biotherapeutic agents for both local and systemic effects.[3]

A diverse class of pharmaceutical and cosmetic products, including creams, ointments, lotions, gels, sprays, and foams, is used to deliver or apply a topical drug on the skin's surface or the mucous membranes.[4] Topical delivery of a drug or any therapeutic agent has been used to induce systemic as well as local pharmacological

effects for treating skin diseases. Local applications of therapeutic compounds are referred to as transdermal drug delivery and have many advantages over oral delivery systems due to the avoidance of the risks associated with intravenous therapy, as well as the elimination of hepatic first-pass metabolism and gastrointestinal incompatibility associated with varying gastric pH. [5] They are applied and used in a wide range, both as skin-care in the form of cosmetics and useful in various dermatological applications, which might be beneficial for both healthy and diseased skin. When these formulations encounter the skin, they form a semi-occlusive layer over the skin surface and release the drug in a controlled manner. [6] Many of these topical treatments restore the pliability of the desiccated horny layer and can also be employed as skin barriers, such as sunscreens and screening agents.[7]

The primary benefits of the topical route are that it is painless and directly delivers the drug to the affected or target site by avoiding the first-pass effect. However, permeation of a drug moiety through the skin from a topical formulation is a multi-step process. It begins with the release of the drug from the dosage form, followed by adhesion or adsorption through the stratum corneum, diffusion through it, and finally absorption into the dermal layer of skin. [8,9] The physicochemical characteristics of topical formulations can determine whether they are liquid, semisolid, or solid. Aside from the active component (drug), each formulation contains a variety of non-medicinal components (excipients) with a range of pharmacological effects and properties. [10,11]

There are numerous treatments and therapies where a range of pharmaceutical products are already available in the market that enhance the appearance and quality when applied on the skin surface or mucous membrane, also restore their fundamental functions, or pharmacologically alter an activity in the targeted tissues, among other things etc. These dermatological or topical medications, which are primarily offered as creams, Lotions and ointments, have several drawbacks, such as stability and friction.[12] The goal of our research is to design a probiotic-based hydrogel and evaluate its gel characteristics and antimicrobial activity against *S. aureus.*

1.1 What are gels?

Gels are semi-solid formulations with a range of characteristics, including softness, toughness, and weakness. Gels can be positioned between the materials in solid and liquid states.[13] When in steady state, this considerably dilute cross-linked system does not exhibit any flow. Gels are dispersions of liquid molecules in a solid matrix.[14] They are designed by trapping significant amounts of aqueous and non-aqueous, such as alcoholic hydrocarbons, in a network of colloidal solid particles that include both inorganic and organic substances.[15] For dermatologic use, the gels possess several advantages such as being greaseless, transparent, easily spreadable, thixotropic, easily transferable, non-staining, emollient, long shelf, bio-friendly, and having an attractive appearance.[7]

Compared to creams and ointments, Gels often provide superior release of drug substance independent of the drug's water solubility. The pharmaceutical and cosmetic industries prepare hydrogels and emulgels that can be used as therapeutic and skincare products. Because of their elegance, gels are widely accepted and used as cosmetics. Hydrogels, which are among all kinds of gels, are three-dimensional hydrophilic structures fabricated made of both natural and synthetic polymers, and are a significant family of gels.[16] Hydrogels exhibit a high ability for swelling in aqueous solutions or water. Since certain human tissues do contain a significant amount of water, the hydrogel-based formulations may resemble human body tissues due to the presence of a large amount of water. This tremendous capacity to swell, hydrogels have an extensive scope of their applications in various biomedical sectors like drug delivery, tissue engineering, and regenerative medicine.[17]

The formulations of these semi-solid preparations for cutaneous application must additionally include anti-microbial preservatives; the preservative chosen must satisfy the need and efficacy in the product as mandated by the relevant authorities or regulatory body. To ascertain or support the preservative's effectiveness for the formulation, numerous appropriate test techniques are needed.

1. MATERIALS AND METHODOLOGY:

2.1 Materials

Levofloxacin is used as a drug obtained from IMTEC (Chandigarh). Sodium CMC (Carboxymethyl Cellulose), HPMC (Hydroxypropyl Methylcellulose), Sodium alginate are three gelling agents used as polymers for the preparation of gel formulations, Tween 80, Glycerine, Propylene glycol are humectants, and Propyl paraben, Methyl paraben are preservatives, all obtained from Hi-Media.

2.1.1 Preparation of gel:

All the ingredients were collected according to the formula given below (**Table 1)** for the preparation of hydrogels using different polymers. The required amounts of gelling agents HPMC, Sodium CMC, and Sodium alginate were added to water, with constant stirring at 500 rpm for about 2-3 hours. A drug was added to the above mixture. Glycerine,

Propylene glycol, Methyl paraben, and Propyl paraben were added to it. The final volume was made with water. All the prepared formulations were allowed to equilibrate for 24 hours at room temperature before performing the evaluation test.

Table 1. Formulation development of an antimicrobial hydrogel.

No.	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Drug (g) (Levofloxacin)	1	1	1	1	1	1	1	1	1
2	HPMC (Hydroxypropyl Methylcellulose) (g)	2	4	6	-	-	-	-	-	-
3	Sodium CMC (g)	-	-	-	2	4	6	-	-	-
4	Sodium alginate (g)	-	-	-	-	-	-	2	4	6
5	Glycerine (ml)	1	1	1	1	1	1	1	1	1
6	Propylene glycol (ml)	1	1	1	1	1	1	1	1	1
7	M ethyl paraben (ml)	.03	.03	.03	.03	.03	.03	.03	.03	.03
8	Propyl paraben(ml)	.02	.02	.02	.02	.02	.02	.02	.02	.02
9	Water	QS	QS	QS	QS	QS	QS	QS	QS	QS

3. EVALUATION OF GELS

The prepared hydrogel formulations were analysed and examined for their appearance and physical properties like colour, homogeneity, pH, swelling index, rheological properties, and antimicrobial activity.

3.1 Homogeneity

The prepared gel formulations consisting of different polymers were evaluated visually for their appearance and their physical properties, like clarity, colours, and phase separation. The formulations are observed or evaluated for the presence of any lumps or aggregates.[18]

3.2 Grittiness

Microscopic observation was done for the presence of any particulate matter in the prepared hydrogel formulations.

3.3 pH measurement

A digital pH meter was used to determine the pH of prepared gel formulations at different temperatures. For this, 1 gram of each formulation was dissolved in 50 ml of distilled water and stored for 2 hours at different temperatures. Every formulation's pH was measured in triplets, and the average values were calculated. [19]

3.4 Spreadability

The Spreadability of the prepared hydrogel formulation containing different polymers was assessed. Placed 1 gram of gel from each formulation in the middle of the lower plates. Another glass plate was then placed over the lower slide. A 100-gm weight was placed gently on glass slides, and after 1 minute for each, the spread diameter was measured. Concentric circles of different diameters before and after placing the weight over the glass slides were drawn on graph paper.[20]

3.5 Drug content

1 gram of levofloxacin taken as a drug in formulation was dissolved in 100 ml of phosphate buffer of pH 5.8. Using a UV spectrophotometer, absorbance was measured at 287-289 λ max nm. A phosphate buffer of pH 5.9 was used to create suitable serial dilutions.[21]

3.6 Swelling Index

The swelling index is determined by taking 1 g of each hydrogel formulation in a porous aluminium foil and placing it in a 50 ml beaker containing 0.1 N NaOH. Then the samples were withdrawn after 24 hours at room temperature and kept for drying, and reweighed.[22]

The swelling index is determined as follows:

Index of Swelling = $\{W_t - W_o / W_o\}100$

Where, after time "t," W_t = Weight of swollen gel

W_o is the weight of gel at zero time.

3.7 Rheological studies and Viscosity measurement

A Brookfield viscometer was used to determine the viscosity of the prepared hydrogel formulation by using a spindle of 62 and 63 at room temperature. After one month, the viscosity of the hydrogel and emulgels formulation was measured by gradually increasing and decreasing the spindle's rotational speed.[23]

3.8 FTIR analysis

The FTIR spectrum of the formulation containing different polymers was obtained using an FTIR spectrophotometer. To record the spectrum in the FTIR spectrophotometer, an adequate number of mixed gel formulations were mixed separately with KBr in the ratio of 1:99. The discs were prepared in a hydraulic press by applying 5.5 tons of pressure. The discs were scanned, and the spectra were calibrated over a wave number range

400- 4000 cm-1. [24]

3.9 Antimicrobial activity

Hydrogels of different polymers, when loaded with an appropriate probiotic, make them a probiotic-based antimicrobial gel. The antimicrobial activity of the prepared gels was evaluated against *Staphylococcus aureus*, the main culprit responsible for the skin diseases and found in large numbers at the wounded site. Hydrogels containing different polymer mixes with the probiotics, including *Lactiplantibacillus plantarum, Lactiplantibacillus pentosus*, and *Bifidobacterium animalis* filtrates, form probiotic gels when spread on the plate containing *S. aureus,* inhibiting its growth by creating inhibition zones. For this, wells containing hydrogels with different polymers loaded with different probiotic filtrates were inoculated over a Mannitol salt agar plate with *S. aureus* growth. The appearance of a zone of inhibition around the wells of a certain diameter after 24 hours of incubation at 37 ⁰ C showed the antimicrobial activities of different probiotic-based hydrogels against *S. aureus.*

Table 2. Physical properties of formulations.

S. No.	Formulation	Homogeneity	Colour
1	HPMC Hydrogel	Smooth and Homogeneous, free from lumps.	Clear transparent
2	Sodium CMC Hydrogel	Smooth and Homogeneous, free from lumps.	Pale yellow
3	Sodium Alginate Hydrogel	Smooth and Homogeneous, free from lumps.	Brown

4. RESULT AND DISCUSSION:

4.1 Visual analysis

The colour, grittiness, and homogeneity of the prepared formulations were examined and analysed visually. All the prepared hydrogel formulations were seen to be clear and transparent. All the gel-based formulations and batches exhibited smooth consistency and good homogeneity, and were free of grittiness and lumps. **(Table 2)** [25]

4.2 Spreadability

The property of spreadability of all gel-based formulations holds a crucial and significant attribute because it ensures precise dosage application to the target site.[26] The diameter of the Spreadability in circles varied from 7.2 cm to 9.7 cm, with HPMC-based hydrogel exhibiting the highest spreadability, followed by sodium CMC and sodium alginate-based hydrogel. The result revealed that the gel's spreadability decreased with increasing gelling agent concentration, as evidenced by the smaller diameter of the circle spread across the plate, and was best given by the gel containing HPMC as polymer. The spreadability diameter of prepared formulations is given in cm **(Table 3)** and diagrammatically shown in **Figure 1**

Table 3. Spreadability of the prepared formulations.

S. No.	Formulations+ Concentration	Spreadability(cm)
1	HPMC (2) Hydrogel	9.1
2	HPMC (4) Hydrogel	9.5
3	HPMC (6) Hydrogel	8.9
4	Sodium CMC (2) Hydrogel	8.7
5	Sodium CMC (4) Hydrogel	8.3
6	Sodium CMC (6) Hydrogel	7.7
7	Sodium alginate (2) Hydrogel	8.5
8	Sodium alginate (4) Hydrogel	8.1
9	Sodium alginate (6) Hydrogel	7.3

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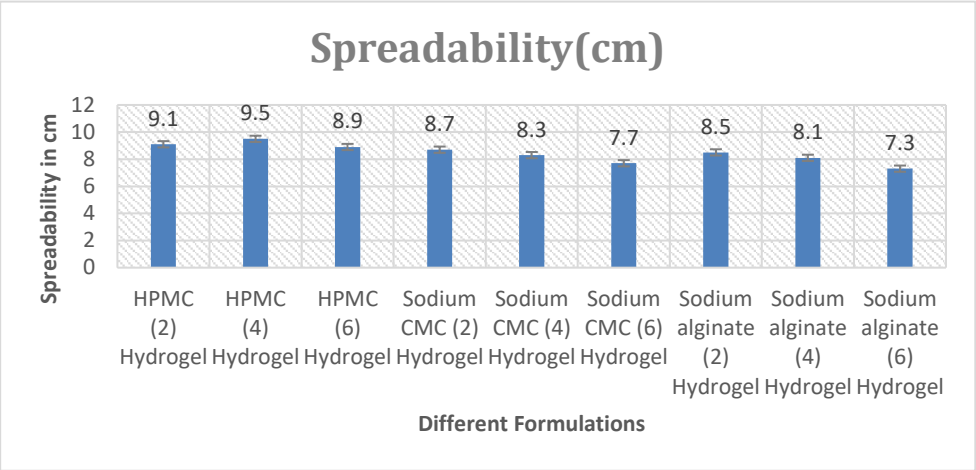

Figure 1. Spreadability of hydrogel formulation.

4.3 pH determination

The pH values of all the prepared hydrogel formulations were in the range of 5.30 to 6.90, which is considered appropriate for the topical pH range of the skin and acceptable to reduce the possibility of skin irritation when administered topically.[27] The pH values of all hydrogel formulations range from 5.19 to 6.73. The pH values of hydrogels with varying concentrations of different polymers at different temperatures are shown in **Table 4** and **Figure 2.**

Table 4. pH evaluation of formulations at different temperatures.

S. No.	Formulations+ Concentration	pH at room temperature	pH at low temperature	pH at high temperature
1	HPMC (2) Hydrogel	6.32	6.18	5.57
2	HPMC (4) Hydrogel	6.64	6.19	5.88
3	HPMC (6) Hydrogel	6.35	6.45	5.19
4	Sodium CMC (2) Hydrogel	6.70	6.03	5.24
5	Sodium CMC (4) Hydrogel	6.71	6.23	5.60
6	Sodium CMC (6) Hydrogel	6.73	6.30	5.70
7	Sodium alginate (2) Hydrogel	5.51	6.10	5.52
8	Sodium alginate (4) Hydrogel	5.60	5.26	5.25
9	Sodium alginate (6) Hydrogel	5.81	6.07	5.42

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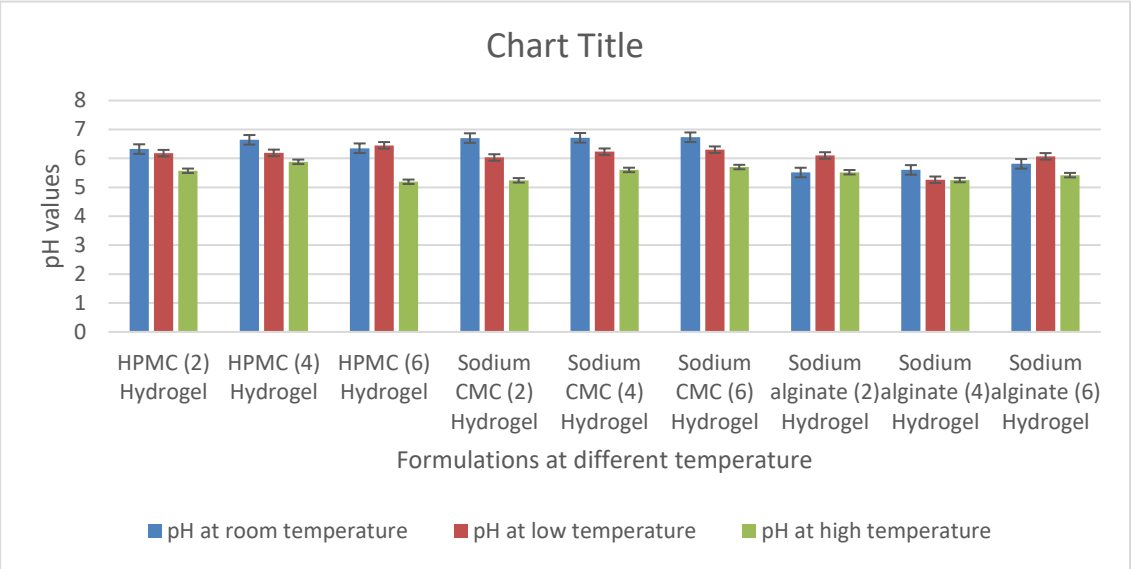

Figure 2. Chart of pH values of formulations at different temperatures.

4.4 Drug content

Levofloxacin, a fluoroquinolone antibiotic, is the optical isomer of the racemic medicinal ingredient ofloxacin. It acts as an antimicrobial agent that obstructs DNA replication by inhibiting the supercoiling activity of bacterial DNA gyrase.[28] It showed a wide range of antimicrobial activity against both Gram-positive and Gram-negative bacteria. It also showed anti-activity against *Mycobacteria* spp., *Chlamydia, Mycoplasma, and Legionella*.[29] It is widely used to treat urinary tract infections, infections of the ear, bones and joints, skin, lungs, and sinuses. It is maximum soluble at pH 5.8-6.6 and minimum at pH 7.0 and above. [30,31] It showed a maximum peak at 298 nm at pH 6.2 (Fig. 3)**.**

On serial dilutions of levofloxacin in phosphate buffer, it was observed that as the concentration of the drug in the buffer decreases, the absorption decreases, as shown in **Figure 4.** The concentration of the drug is directly proportional to the absorption at 298 nm.

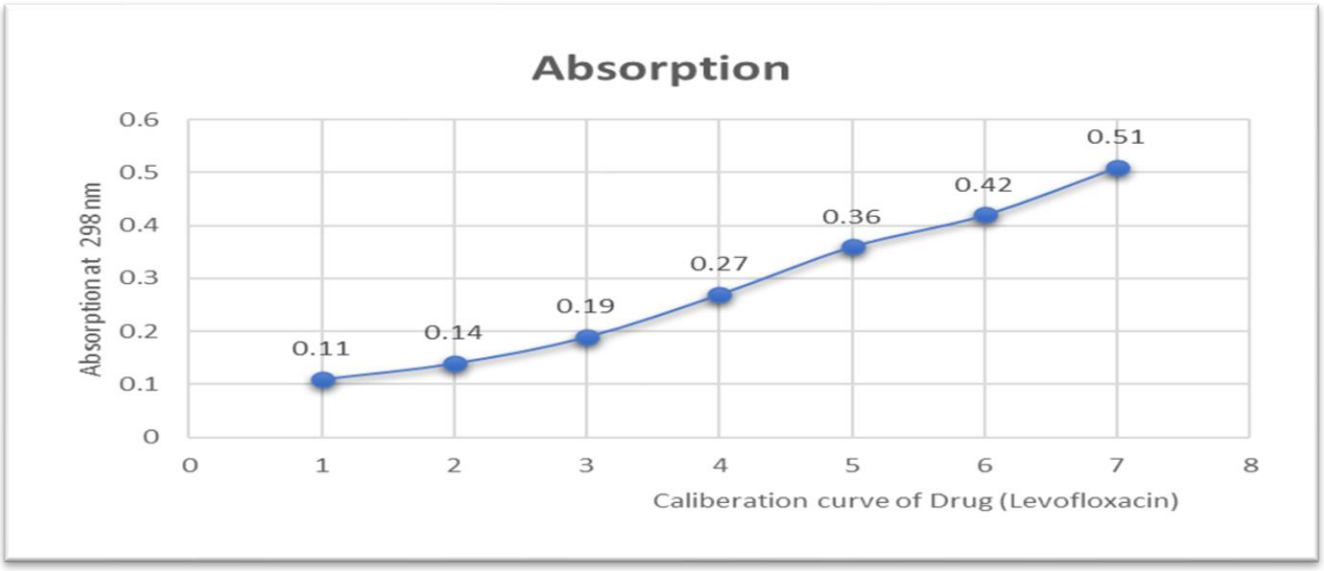

Figure 3. Calibration Curve of Levofloxacin at 298 nm.

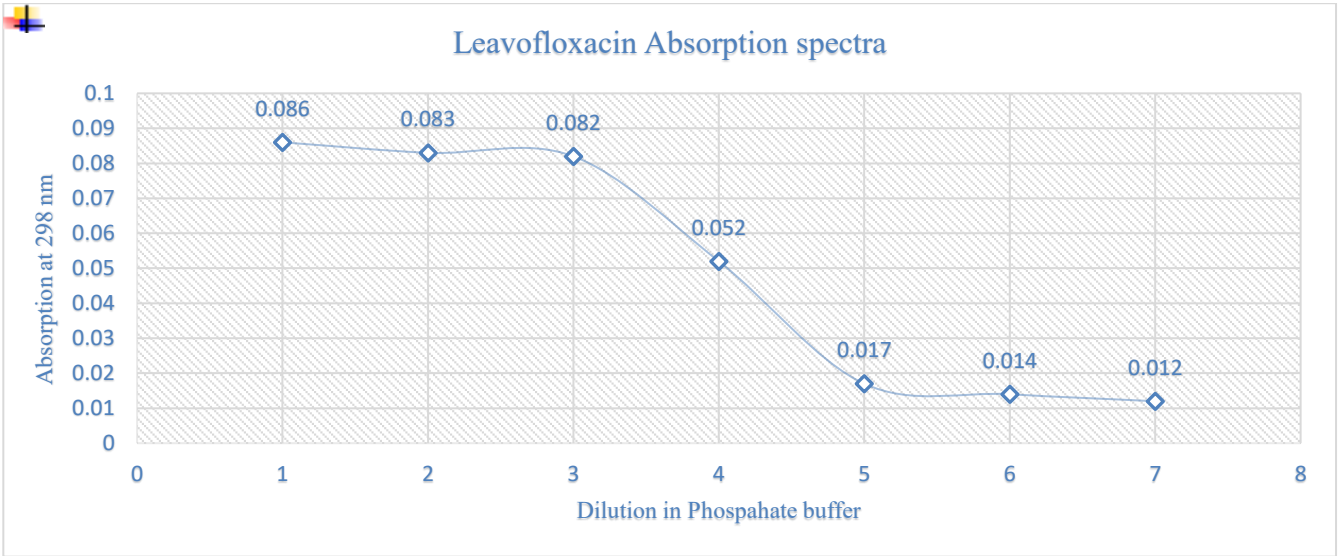

Figure 4. The graph shows the absorption of Levofloxacin dissolved in different concentrations in Phosphate buffer at pH 6.2.

4.5. Rheological properties

The determination of rheological properties like viscosity, spreadability, and swelling index is vital in assessing its functionality and possible applications. It is used for the assessment of physical stability and is used as a topical preparation during storage and application.[32] From the studies, it was revealed that viscosity increases as the concentration of each polymer used in the hydrogel increases. And in the case of swelling index, the value ranges from 118 % to 301% after 24 hours of incubation at room temperature. The viscosities and swelling index of all the formulations are shown in **Table 5.**

Table 5. Measurement of Viscosity and Swelling index of hydrogels of different polymers.

S. No.	Sample	Viscosity (cpc)	Swelling index (%)
1	HPMC (2) Hydrogel	5237	119%
2	HPMC (4) Hydrogel	7948	118%
3	HPMC (6) Hydrogel	**9718**	130%
4	Sodium CMC (2) Hydrogel	5329	216%
5	Sodium CMC (4) Hydrogel	6798	222%
6	Sodium CMC (6) Hydrogel	**8506**	172%
7	Sodium alginate (2) Hydrogel	5809	177%
8	Sodium alginate (4) Hydrogel	7332	238%
9	Sodium alginate (6) Hydrogel	**8113**	301%

4.6 Antimicrobial activity of probiotic-based hydrogels.

Nowadays, hydrogels are considered an effective formulation for transdermal drug delivery; therefore, broadly applied in many biomedical-associated contexts. Hydrogels loaded with probiotics or any other antimicrobial agent have antimicrobial properties; their hydrated polymeric networks possess the ability to eliminate harmful microbes that can be used in pharmaceutical applications, including disinfectants, sanitizers, medications, and personal care products to treat wounds and other dermal infections. Probiotics can help with wound healing by reducing inflammation, promoting collagen deposition, and killing pathogenic bacteria. Hydrogels can deliver probiotics to wounds and maintain their stability and viability for a longer duration.[33] The hydrogels with different polymers loaded with the probiotics *Lactiplantibacillus plantarum, Lactiplantibacillus pentosus,* and *Bifidobacterium animalis* isolated from honey, tomato, and banana, respectively, showed antimicrobial activity against *S. aureus* by forming a zone of inhibition. From the zone of inhibition, it was interpreted that hydrogel polymers loaded with *Lactiplantibacillus plantarum* showed good antibacterial activity in comparison to other probiotics-loaded gels, as given in **Table 6.**

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Table 6. Antimicrobial activity of hydrogels loaded with probiotics.

S. No	Gels + Probiotics	Zone of inhibition against *S. aureus* (mm)
1	HPMC + *L. plantarum*	**18**
2	HPMC + *L. pentosus*	**13**
3	HPMC + *B. animalis*	**11**
4	Sodium CMC + *L. plantarum*	**17**
6	Sodium CMC + *L. pentosus*	**15**
7	Sodium CMC + *B. animalis*	**12**
8	Sodium alginate + *L. plantarum*	**18**
9	Sodium alginate + *L. pentosus*	**12**
10	Sodium alginate + *B. animalis*	**14**

4.7 FTIR graphs of different formulations.

- Multiple distinctive bands or peaks for various polymers utilized as gelling agents were visible in the image displaying the FTIR spectrum.
- The FTIR spectrum shows characteristic peaks in the range 3300-3370 $cm^{-1,}$ indicating the presence of a carboxylic group.
- Peak at range 1600-1650 cm^{-1} exhibits alkenes, 1400-1420 cm^{-1} exhibits the presence of aromatic rings.
- Peaks at 1342 cm^{-1} and 1396 cm^{-1} indicate the presence of alkyl halides and carboxylic acids, respectively.
- Peaks or bands at 1227 cm^{-1},1273 cm^{-1}, and 1311 cm^{-1} indicate the presence of amine oxide, alkyl halides, and ester, respectively.

4.7.1 The FTIR graph of HPMC-based hydrogel showed the peaks or bands: (Fig. 4)

- The peak around 3300 cm^{-1} O-H stretching vibration of the hydroxyl group.
- Intense peak at 1049 cm^{-1} is due to C-O stretching.
- Peak at 1375 cm^{-1} indicates the presence of C-O-H bending vibrations of hydroxyl group.[34]

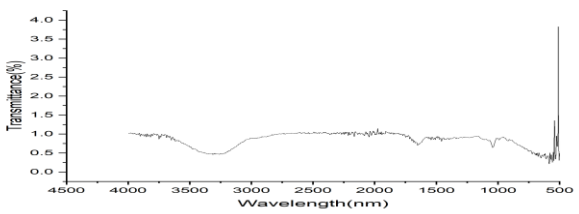

Fig 4. FTIR graph of HPMC-based hydrogel.

4.7.2 The FTIR graph of Sodium alginate-based hydrogel showed bands or peaks at different wavelengths: (Fig. 5)

Peaks are observed at 3315 cm^{-1} attributed to O-H stretching.

The band at 1030 cm^{-1} is due to C-O-C stretching.

Peak at 1600 cm^{-1} indicates C=O stretching.[35]

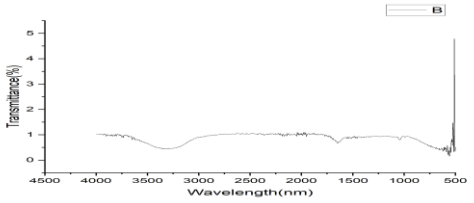

Fig 5. FTIR graph of Sodium alginate-based hydrogel.

4.7.3 The FTIR graph of Sodium CMC-based hydrogel showed bands or peaks at different wavelengths: (Fig. 6)

The broad band between 3430 and 2900 is attributed to O-H stretching due to the presence of many hydroxyl and carboxyl groups in CMC.

Band at 1609 can be attributed to C=O, the carboxyl groups.

Peaks at 1068 represents C-O-C stretching vibrations.[36]

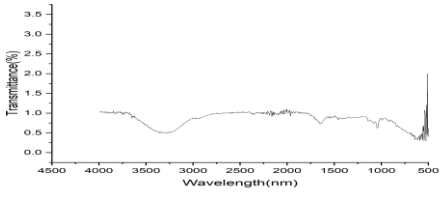

Fig 6. FTIR graph of Sodium CMC-based hydrogel.

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