FORMULATION DEVELOPMENT, OPTIMIZATION, AND EVALUATION OF A SUSTAINED-RELEASE HYDROGEL SYSTEM OF EMPAGLIFLOZIN USING ALMOND AND NEEM GUMS

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ABSTRACT
The research proposes a sustained-release hydrogel formulation of Empagliflozin using natural polymers like almond gum and neem gum as biodegradable and biocompatible carriers. The drug delivery system aims to optimize the therapeutic efficacy in the management of Type 2 diabetes, and the hydrogel system controls the release of the drug for 24 hours, thereby improving patient compliance. FTIR and DSC analysis revealed that the two gums were compatible with each other. In the in-vitro study, it was established that each of the two gums showed distinct release profiles, and neem showed a slower release with a more extended release. This work demonstrates the potential for natural gums, almonds and neem as alternate latexes to synthetic polymers for sustained-release drug delivery systems with environment friendly and biocompatibility benefits. In-vivo efficacy will be further explored.
KEYWORDS: Sustained-release hydrogel, Empagliflozin, Almond gum, Neem gum, FTIR analysis, Crosslinked hydrogels, Natural gum hydrogels,

INTRODUCTION

Long-acting drug formulations maintain therapeutic levels, require less frequent dosing, and improve patient compliance. These systems release medications over an extended period, minimizing drug concentration fluctuations and enhancing efficacy. Natural polymers like almond gum and neem gum are popular due to their biocompatibility, biodegradability, and low toxicity. These sustainable and safer alternatives to synthetic polymers are increasingly being used in chronic conditions management (Craciun et al., 2019). Hydrogels, made from natural polymers, are advantageous in drug delivery due to their ability to hold large amounts of water, providing a soft biocompatible matrix. They are useful in wound healing, drug delivery, and tissue engineering. Empagliflozin, an SGLT2 inhibitor for Type 2 diabetes, works independently of insulin (Peers et al., 2020). The research aims to create a sustainable, biocompatible hydrogel system for Empagliflozin using natural polymers like almond and neem gum (Hennink & Nostrum, 2002). These gums offer controlled swelling, stability, and high drug entrapment efficiency, making them ideal for drug delivery (Rosiak & Yoshii, 1999). This could lead to further use of natural polymers in sustained release drug delivery.

HYDROGEL:

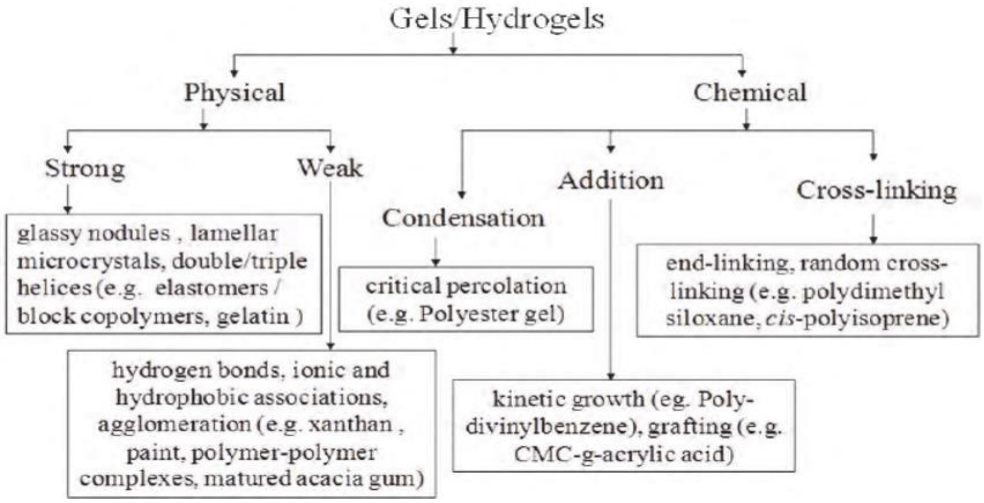


Fig.1: Classification of gelation mechanism and relevant examples

Hydrogels are highly absorbent polymer chains that can hold large amounts of water or biological fluids, retaining up to 99% of their weight in water (Rosiak & Yoshii, 1999). They have gained popularity in biomedicine due to their compatibility with biological systems.

MATERIALS AND METHODS

"Material from pre-formulation" study on preparation, optimization and evaluation techniques is employed in the present work to develop a sustained-release hydrogel system incorporating Empagliflozin employing almond and neem gums. These all steps would be crucial for the final "hydrogel formulation" to maintain its stability, biocompatibility, and drugs delivery protracted period.

MATERIALS

The Empagliflozin API was utilized in this study, along with natural polymers from almond gum and neem gum, which possess hydrophilic, biocompatible, and biodegradable properties, making the hydrogel formulation suitable for this polymer network (Li et al., 2021). Glutaraldehyde or epichlorohydrin stabilize the matrix and control hydrogel mechanical properties, while solvents like distilled water and methanol are used for purification or formulation preparation.

EVALUATION OF GUMS:

Drug-Excipients Compatibility:

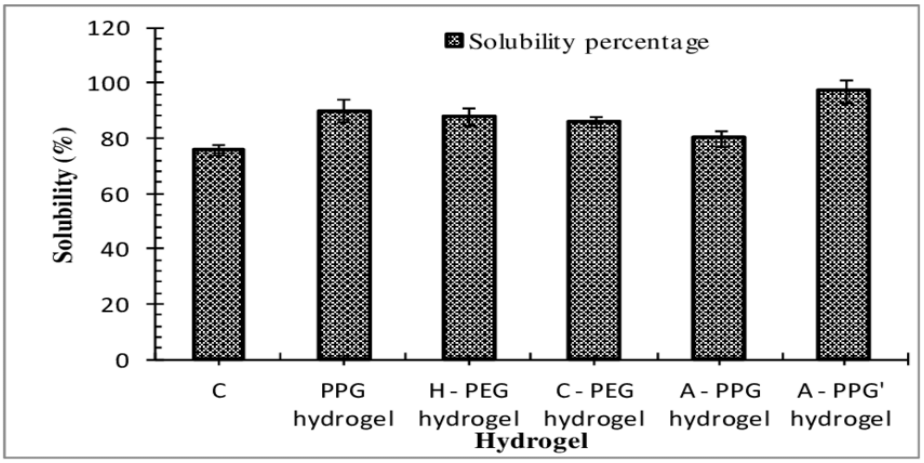


Fig.2: Solubility Percentage
(Source: Kumaran et al., 2017)

The compatibility of Empagliflozin and natural gums is ensured through Fourier Transform Infrared Spectroscopy and Differential Scanning Calorimetry, ensuring no unwanted reactions that could affect the formulation's stability or effectiveness (Peers et al., 2020). FTIR identifies changes in peaks and bond formation, indicating chemical interactions with gums. DSC measures Empagliflozin's thermal stability and phase transitions in gum presence, detecting changes in melting points or heat flow patterns that may indicate incompatibility.

Characterization Of Gums:

Natural polymers are almond and neem gums. Complex polysaccharide structures are a primary attribute of these gums. From there, the first thing is the extraction and purification of gums. Almond gum was obtained from the bark of Prunus dulcis, which was purified to get rid of any extraneous materials (Zhang et al., 2020). Neem gum obtained through natural or induced injury on Azadirachta indica was purified the same way. The chemical composition of all the gums is primarily polysaccharides, with almond gum mainly arabinogalactan and neem gum polysaccharides of a backbone type like tetranortriterpenoid compounds.

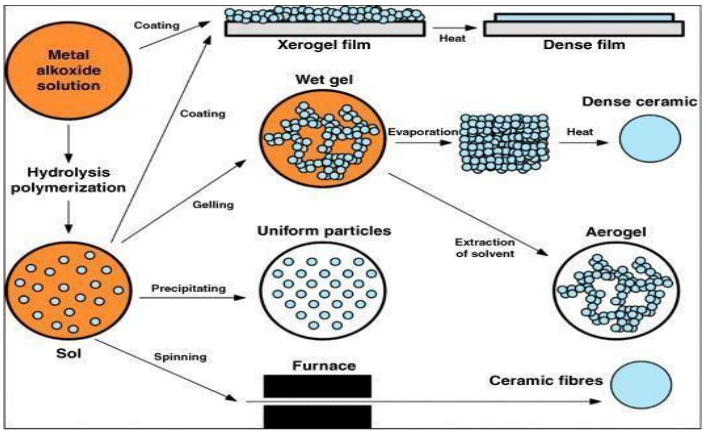


Fig.3: Gel process
(Source: Shirisha et al., 2019)

Crosslinking techniques, like chemical crosslinking with glutaraldehyde, strengthen the hydrogel's

three-dimensional network by introducing covalent bonds between polysaccharide chains. Physical methods like heat treatment can increase gel viscosity and stability without introducing reactive agents, improving water-holding capacity and mechanical resiliency. This enhances the gums' performance as drug delivery matrices.

Preformulating Studies:

The pre-formulation phase of drug development involves evaluating the drug's physical attributes and content to determine dosage, administration method, and chemical characteristics. Analytical techniques like infrared, UV, and melting point spectroscopy were used to identify the drug sample. The study also examined solubility, partition coefficient, and drug-excipient interaction using FT-IR spectra.

Preparation of Hydrogel sphere:

The hydrogel formulation is created by dispersing almond and neem gums in distilled water, each with a unique structural characteristic. The drug is then charged into the polymer solution, and glutaraldehyde crosslinks the drug-loaded mixture to control the drug release rate and optimal entrapment with slow release of Empagliflozin.

Table No.1: Composition of different concentrations of almond gum, neem gum and glutaraldehyde.

Sr. no.	"Almond Gum (% w/v)"	"Neem Gum (% w/v)"	"Glutaraldehyde (% v/v)"	"Empagliflozin (mg)"	"Distilled Water (mL)"
F1	1.0	1.0	0.5	50	10
F2	1.5	0.5	0.5	50	10

F3	0.5	1.5	0.5	50	10
F4	1.0	1.0	1.0	50	10
F5	1.5	0.5	1.0	50	10
F6	0.5	1.5	1.0	50	10
F7	1.0	1.0	1.5	50	10
F8	1.5	0.5	1.5	50	10
F9	0.5	1.5	1.5	50	10
F10	1.0	1.0	2.0	50	10

EVALUATION OF HYDROGEL SPHERE:

Appearance:

It was done by using visual observation of all formulations.

Entrapment efficiency [40]:

To calculate the hydrogel sphere's encapsulation efficiency, an ultra-filtration method was used. After diluting the prepared hydrogel with water, 1 mL of the diluted hydrogel sphere was added to the top of a centrifuge tube that had an ultrafilter attached, and the tube spun for 30 minutes at room temperature at 6000 rpm. As previously indicated, the filtrate containing unencapsulated drug was "collected and subjected" to "UV analysis at 224 nm". The percentage of encapsulation "efficiency was calculated" indirectly "using the following equation":

$$EE\ \% = \frac{\text{“Initial amount of drug”} - \text{“Final amount of drug”}}{\text{“Initial amount of drug”}} \times 100$$

Particle size and zeta potential determinations:

The Zeta sizer Nano device was utilized to measure the particle size (PS) and zeta potential of drug-loaded hydrogel sphere, while photon correlation spectroscopy and electrophoretic mobility were also employed. Prepared hydrogel sphere was diluted 100 times, added to the sample cell, and positioned inside it to measure the Zeta potential and particle size, respectively [41].

SEM:

The hydrogel sphere compound's surface morphology was examined using SEM. After utilizing a gold sputter module to coat the hydrogel sphere on adhesive tape attached to an aluminum stub, the coated sample was scanned, and SEM photomicrographs were captured.

SWELLING INDEX:

The polymer's ability to swell is influenced by the polymer's concentration, ionic strength, and watercontent. Initial weight of the films was taken, and they were subsequently submerged in freshly made artificial tear fluid pH 7.4 at 37°C to calculate the swelling index. After 90 minutes, the films were taken off the plate, the surface water was wiped off using filter paper, and the films were reweighed. The swelling index was determined.

"Swelling index (%) = (Wt –W0)/(W0) X 100"

"Where W0 is the initial weight of the sample and Wt is its weight at time t."

IN VITRO DRUG RELEASE STUDIES:

To investigate the drug release properties from hydrogel sphere, a Franz diffusion cell was used. A cellophane diffusion barrier separates the donor and receptor compartments in the cells. There is room for 18 ml in the receptor compartment. Simulated tear fluid (STF), which has a pH of 7.4, was inserted into the receptor compartment. The entire assembly was stirred at a speed of 100 rpm while maintaining a temperature of 37.0 0.50C using a magnetic stirrer. The donor compartment was spun with the 1g samples, which are equivalent to 1mg of medication, suspended across the membrane. The receptor compartment's 1 ml samples were periodically removed, and the container was then filled with the same volume of diffusion medium. When introducing diffusion medium to the receptor compartment, it was carefully avoided trapping air behind the diffusion barrier. The samples were sent for a spectrophotometric examination after the requisite dilutions (Ciolacu et al., 2020). After the drug release was calculated, a visual showing drug release relative to time was created. Each formulation's release experiments were performed in triplicate.

RESULT AND DISCUSSIONS:

It presents the results of the three successive stages of the sustained-release hydrogel system with the pharmaceutical Empagliflozin in combination with the natural polymer systems, namely almond gum and neem gum. The results are elaborated with key points: hydrogel characterization, drug release pattern, in-vivo application, and merits and drawbacks of using the two natural polymer systems.

Characterization of Hydrogels FTIR and DSC Studies:

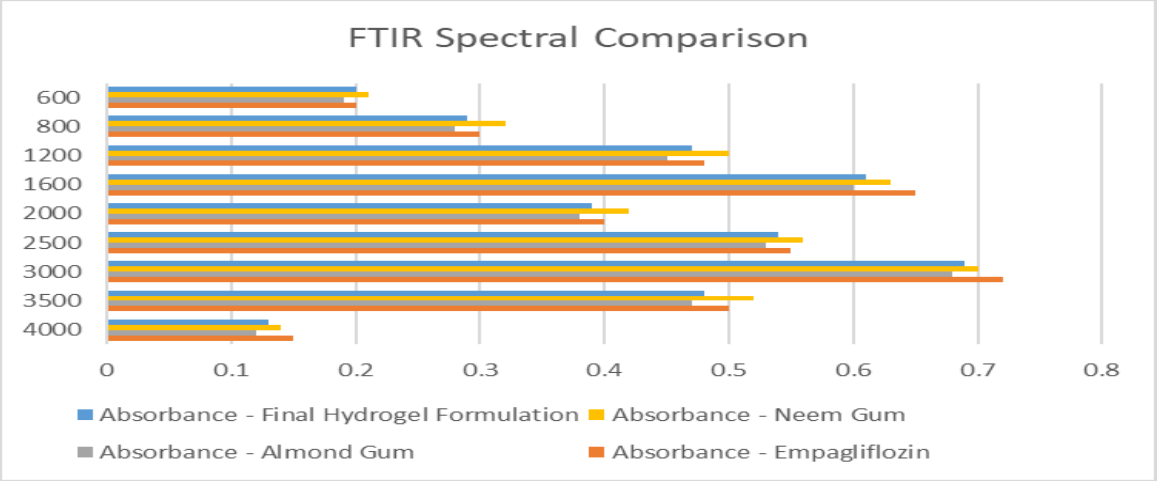


Fig.1: FTIR Spectral Comparison

FTIR and DSC analyses were used to check the suitability of the gums for co-blending with Empagliflozin and ensure no component integrity was affected. In the FTIR, characteristic peaks of Empagliflozin remained unaffected and in a similar position following mixture preparation: carbonyl bond absorption is found at 1,600–1,700 cm^{-1}. In comparison, C-O bonds lie at 1,200 cm^{-1}. The lack of any chemical interaction, which would significantly affect the hydrogel matrix, from which the structure of the incorporated drug Empagliflozin was concerned, has been supported by the data obtained from DSC (Zou et al., 2020). The melting point of the drug was about ~154°C, which is similar in line with literature values and no additional exothermic peaks or endothermic could be seen, which meant Empagliflozin itself was not incompatible with any of the natural gums.

PREFORMULATION STUDY:

Organoleptic properties:

Organoleptic properties of drug Empagliflozin was found to be as per literature. The Organoleptic properties of Empagliflozin found to the given in Table 5.1

Table No. 5.1: Organoleptic properties of Empagliflozin

Sr. No.	Properties	Description
1	Odour	Sweet smell
2	Colour	Pale Yellow
3	Taste	sweet or metallic taste

Melting Point:

Drug name	Observed M. P	Reference
Empagliflozin	151.3 ℃	151-153℃

Calibration curve of Empagliflozin in methanol:

Determination of absorption maxima by UV spectroscopy:

Figure 5 shows the results of the Empagliflozin UV spectrum analysis.

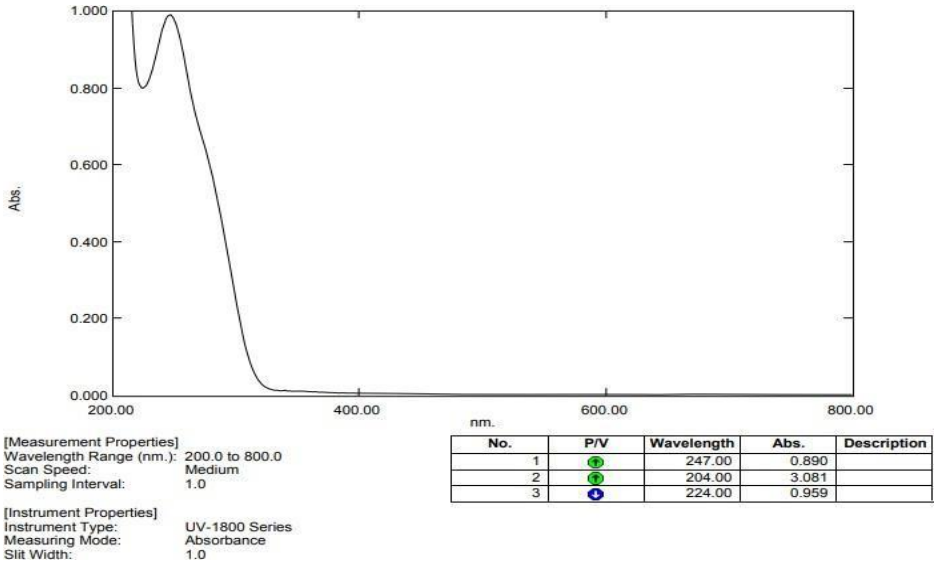


Fig.4: UV spectrum of Empagliflozin.

Table No. 5.3: Absorption maxima (λ_{max}) of Empagliflozin.

Name of drug	Absorption maxima (λ_{max})	
	Observed	Reference
Empagliflozin	224 nm	224nm

Discussion: Empagliflozin was determined to have a maximum wavelength of 207 nm, which agrees with reference standards.

Preparation of calibration curve of Empagliflozin in Methanol [107]:

A 100µg/ml of Empagliflozin standard stock solution was made using Methanol. This solution was diluted to the appropriate concentrations (2–10/ml) with methanol before being analyzed spectrophotometrically at 207nm. Figure 7.2 and Table 5.4 below both graphically display the results.

Table No. 5.4: Calibration curve of Empagliflozin in Methanol

Sr.no.	Concentration µg/ml	Absorbance
1	2	0.183±0.002
2	4	0.367±0.002
3	6	0.542±0.002
4	8	0.764±0.002
5	10	0.966±0.002

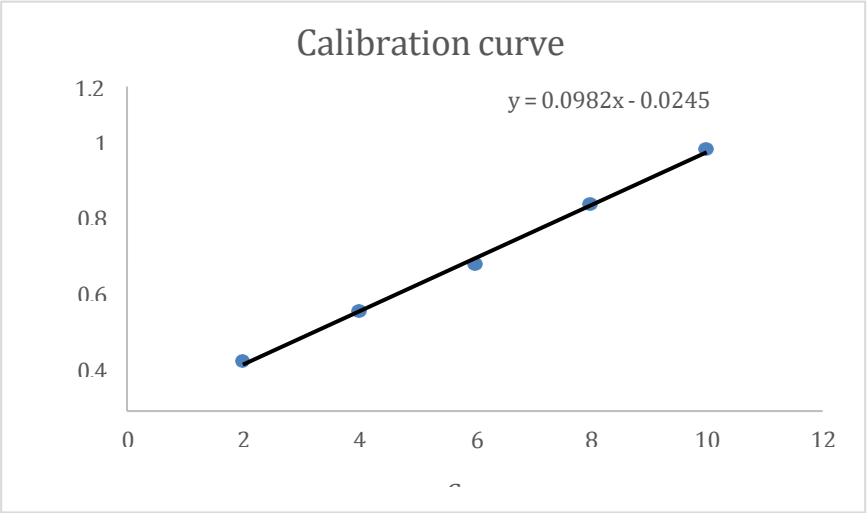


Fig.5: Calibration curve of Empagliflozin in Methanol

Discussion: With Empagliflozin concentrations ranging from 2 to 10µg/ml, methanol was used to generate the calibration curve for Empagliflozin. At 207 nm, the absorbance was determined. The standard curve for Empagliflozin is shown in table 5.4. The regression equation is given by = 0.0982x - 0.0245 and the R2 value is 0.9981, indicating good linearity.

Partition coefficient determination [108]:

The shake flask method was used to carry out an investigation on partition coefficient determination. Table 5.5 displays the partition coefficient of Empagliflozin.

Table No. 5.5: Partition coefficient of Empagliflozin

Drug	Solvent system	Log P Values
Empagliflozin	n-octanol: water	1.28± 0.020

(Mean ± SD, n=3)

Discussion: The partition coefficient of Empagliflozin in n-Octanol: Water; was found to be 1.28±

0.020 consistent with the literature. This exhibits that Empagliflozin has lipophilic properties.

Solubility studies:

The observed solubility profile of the drug is shown in Table No. 5.6.

Table No. 5.6: Solubility profile of Empagliflozin in different solvent

Sr. no.	Solvent	Solubility (mg/ml)
1	Ethanol	9.039±0.148
2	Methanol	10.101±0.201
3	Dimethylformamide	6.395±0.085
4	DMSO	5.054±0.223
5	Water	0.696±0.141

(Mean ± SD, N=3)

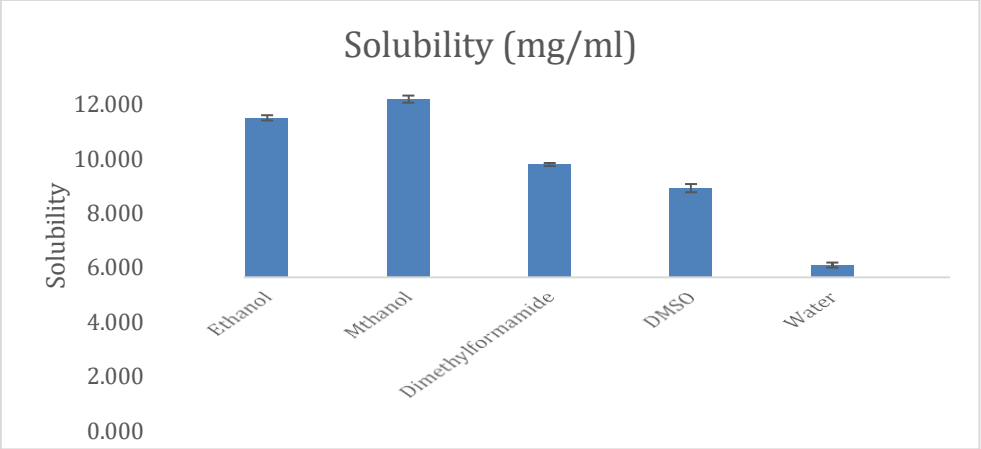


Fig. 6: Solubility profile of Empagliflozin in different solvents

Discussion: Figure 5.3 and Table 5.6 in the information mentioned data shows that Empagliflozin is freely soluble in methanol and soluble in ethanol, DMSO, and dimethyl formamide and insoluble in water.

Evaluation of Hydrogel sphere:

Visual appearance:

Table 5.12: Visual examination of hydrogel (F1-F10)

Sr. No	Formulation Code	Appearance
1	F1	clear or translucent
2	F2	clear or translucent
3	F3	clear or translucent
4	F4	clear or translucent
5	F5	clear or translucent
6	F6	clear or translucent
7	F7	clear or translucent

8	F8	clear or translucent
9	F9	clear or translucent
10	F10	clear or translucent

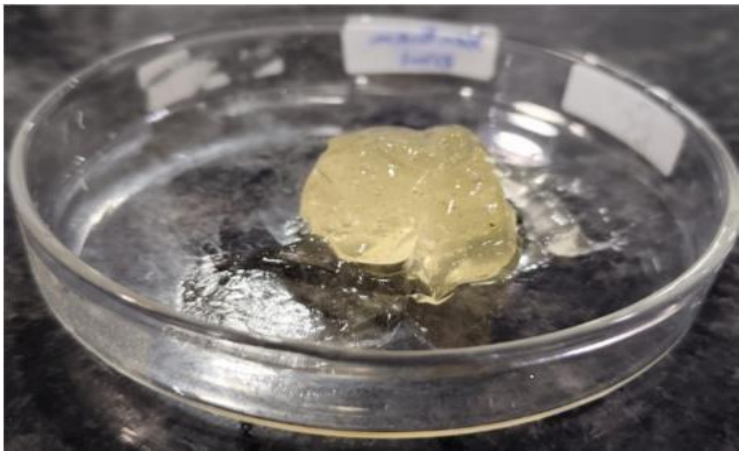


Fig. 7: Visual Appearance of hydrogel

Entrapment Efficiency

Table 3: Entrapment Efficiency of Formulation F1 to F10

Sr. No	Formulation Code	%Entrapment Efficiency
1	F1	54.43±0.234
2	F2	61.67±0.319
3	F3	66.45±0.120
4	F4	71.617±0.251
5	F5	76.651±0.653
6	F6	81.34±0.765
7	F7	87.34±0.329
8	F8	92.312±0.653
9	F9	90.356±0.672
10	F10	88.81±0.342

Particle size:

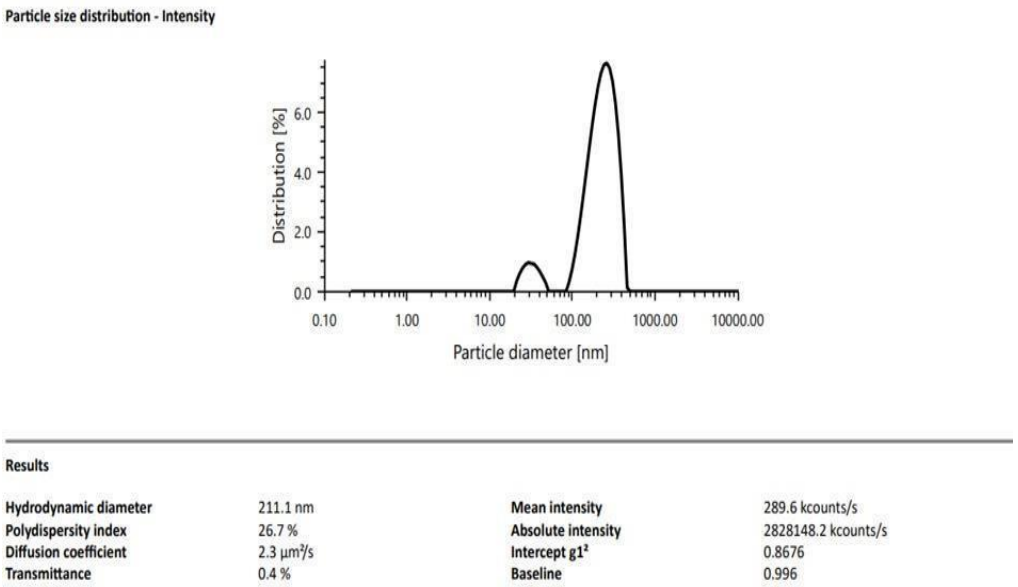


Fig. 8: Particle size of Formulation F8

Discussion: This graph provides particle size distribution results using dynamic light scattering (DLS). This intensity-based distribution also brings out a high degree of particle density at around 100 nm, which is reflected on the graph. The size distribution characterizations include hydrodynamic diameter of 211.1 nm, polydispersity index of 26.7% which indicates moderate polydispersity and diffusion coefficient of 2.3 µm²/s. Low transmittance (0.4%) gives a high turbidity value. Mean and peaks intensities for the samples are 289.6 kcounts/s and 2,828,148.2 kcounts/s respectively. The intercept and baseline values are also satisfactory: 0.8676 and 0.996 respectively, which suggests the fact that the data collected for this study is of high quality. These metrics describe the properties of particle size and particle size distribution of the sample.

Zeta potential:

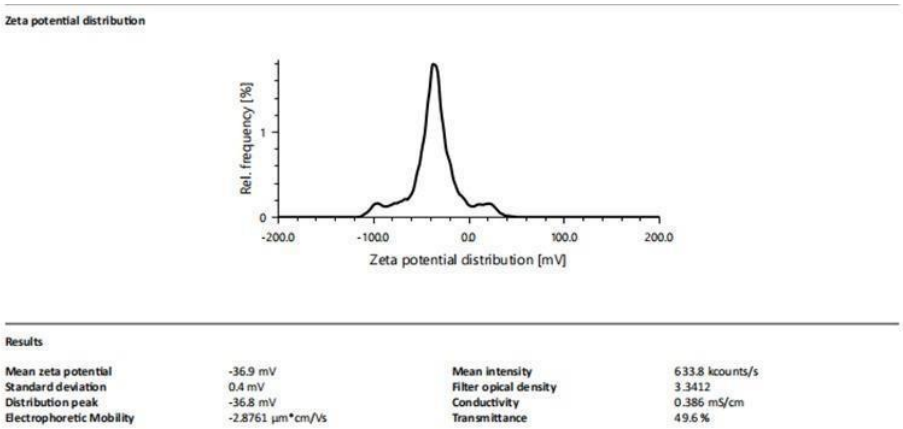


Fig. 9: Zeta potential of Formulation F8

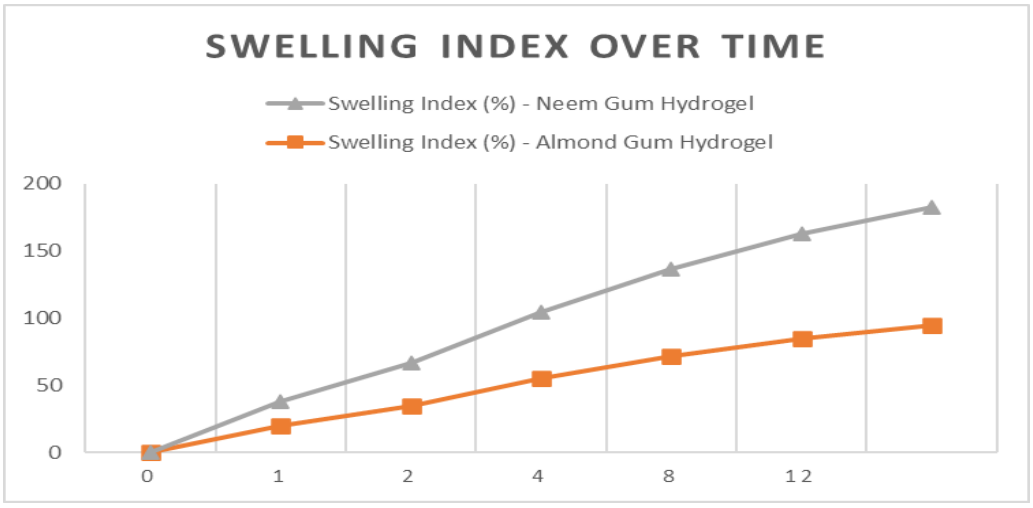
SEM:

Physical Properties of Hydrogels:

Hydrogels were evaluated regarding viscosity, gel strength, and swelling capacity. Crosslinking increased the viscosities of almond and neem gum, with a higher value indicating more strength and connectivity in their networks. Increased viscosity prevents the rapid diffusion of water or drug molecules; thus, crosslinking is necessary for prolonging the drug release for longer periods (Bayer, 2021). The gel strength testing indicated that the hydrogels prepared with neem gum were stronger than those prepared with almond gum. It is perceived that neem gum contains more cross-linkable functional groups in its composition, thus allowing for a denser network. Crosslinking enhances the resilience of the hydrogel under mechanical stress, which confirms its suitability for sustained release applications.

Fig 2: Swelling Index

(Source: Self-created)



Immersing samples in a buffer solution determined the swelling capacity of the hydrogels. Neem gum hydrogels showed a slightly higher swelling index than almond gum, which is due to the higher hydrophilicity of neem gum. The swelling index is an important factor for drug release since the higher index often corresponds to a higher rate of release, as the increased permeability of the hydrogel network is observed (Zou et al., 2020). The swelling behavior has been affected by the density of crosslinking. The more crosslinked the networks were, the more that did not swell; nevertheless, they provided longer drug releases because of the slower rate of diffusion.

In vitro drug release study:

The in-vitro release studies were performed to study the sustained-release behaviour of Empagliflozin from the hydrogel matrix. Cumulative release data exhibited controlled release over 24 hours (Kass and Nguyen, 2022). It started with a small burst release phase, possibly due to the drug particles present on the surface of the hydrogel diffusing out quickly, but then the release rate became steady and reached a sustained profile with both gums.

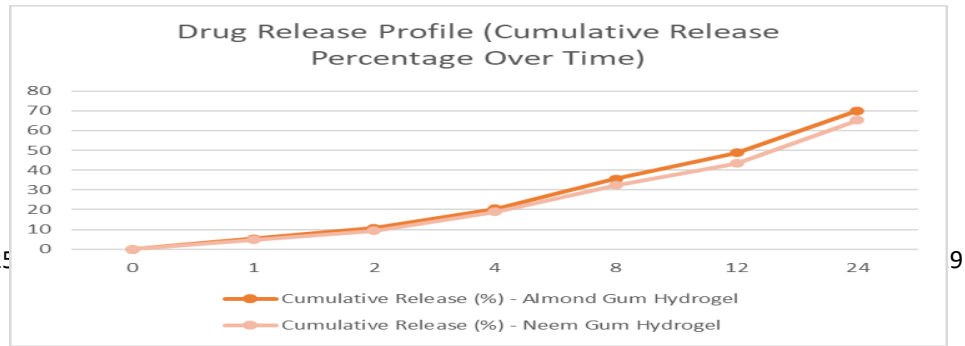


Fig. 4: Drug Release Profile

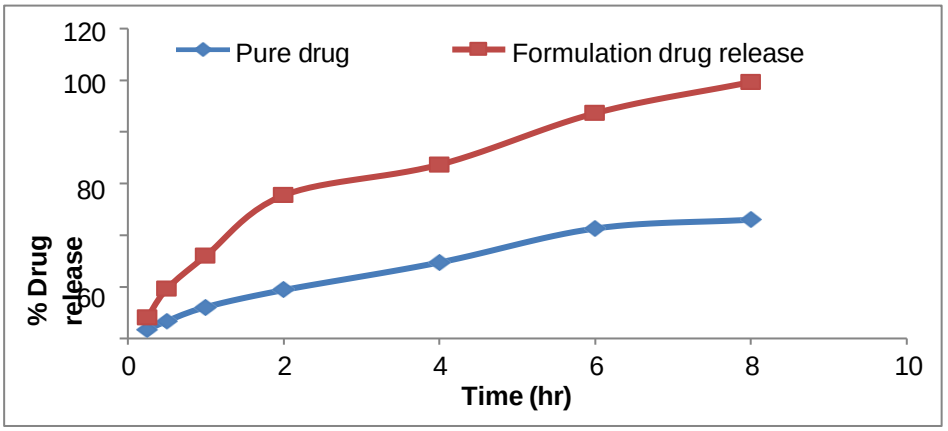


Fig. 5: Drug Release Profile

In the case of hydrogels prepared with almond gum, the release rate was found to be about 70% in 24 h, and about 65% release in the same duration for hydrogels of neem gum. In this respect, slower drug release can be visualized for neem gum compared with almond gum, probably because the former has a strong, denser gel matrix that slows down diffusion in the hydrogel (Vigata et al., 2020). Sustained-release objectives were adequately met with excellent alignment between the release profiles and original expectations regarding a hydrogel matrix for long-term drug delivery.

Influence of Gums:

Both almond and neem gums showed different properties in the contribution to release profiles, meaning that both had distinct properties. The drug released from almond gum has lower gel strength and moderate viscosity and is released slightly faster. This shows that almond gum would be a better candidate for applications that require a shorter duration of release (Huang et al., 2022). However, the denser structure and higher viscosity of neem gum better served in applications involving longer-term drug release since its structure more favorably controls water and drug molecule permeation rates(Amiri et al., 2021). Such variations in the structural properties of such natural gummies may often highlight that the type selected may well depend upon application requirements to obtain specific desirable traits.

$$\text{Fraction Released} = \frac{Qt}{Q\infty}$$

ADVANTAGES AND DISADVANTAGES OF NATURAL POLYMERS:

Advantages of Almond and Neem Gums:

Almond and neem gums can be used as natural polymers in drug delivery systems; there are many advantages to that. Both are biodegradable and biocompatible, thus adhering to the idea of achieving better pharmaceutical products about safety and environment-friendly principles (Malabadi et al., 2021). Synthetic polymers can produce toxic residues after getting degraded, thus not favourably affecting the biological side during degradation. These are their very high hydrophilicity and excellent potential to crosslink. As a result, almond and neem gums will prove to be an ideal choice as a component in hydrogels. They are inexpensive and readily available, and they contribute to increased economic viability.

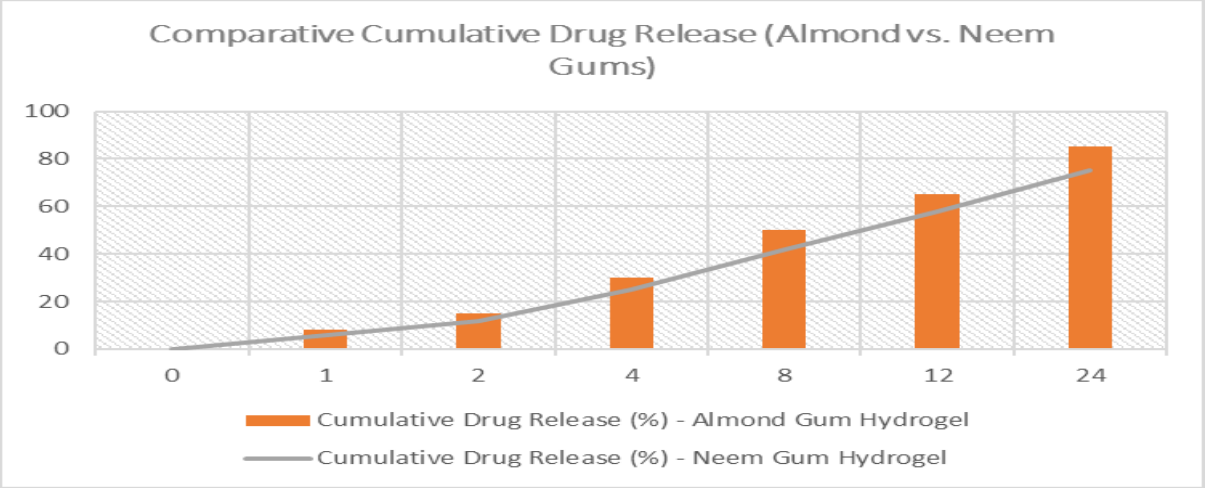


Fig.7: Comparative Cumulative Drug Release (Almond vs. Neem Gums)
(Source: Self-created)

Both gums have bioactivity neem and, in fact, have crosslinking without erosion of their antimicrobial activity and anti-inflammatory properties; further therapeutic advantages could be obtained when drug delivery systems are employed. The property shown by the hydrogels above to maintain their integrity up to long times with controlled release further gives credence to the pragmatic uses these gums have in long-time formulae.

Drug Release Rate Constant for Zero-Order Kinetics:

If a zero-order release (constant release rate) is achieved, the rate can be represented as:

$$C_t = C_0 + K_0 \times t$$

where:

- C_t: Concentration of Empagliflozin in plasma at time t,
- C_0: Initial concentration,
- K_0: Zero-order release rate constant.

Limitations of Natural Polymers:

The challenges in using almond and neem gums are the limitations despite these advantages. The most significant drawback of these natural polymers is batch-to-batch variability, which is brought about by environmental factors impacting the chemical composition of the gums. Variability in gum composition can be one of the causes of variability in gel strength, swelling index, and drug release behavior, making standardization of formulation difficult (Alwossabi et al., 2021). Contamination with microorganisms also poses a problem with the use of natural polymers since they are exposed to the external environment during harvest. High purification steps are needed in the final steps of impurities removal and may add additional time and expenses to the manufacturing process. Furthermore, as crosslinking increases stability in the hydrogel, it tends to compromise some degree of their natural bioactivity within the polymers. For instance, neem gum may lose a stronger antimicrobial attribute during overly chemical crosslinking. The problem has been the formulation itself, balancing crosslinking and stability with no absolute loss of bioactivity. Despite such limitations, proper processing and quality control can indeed elevate almond and neem gum to considerable potential toward sustainability in biocompatible drug delivery systems.

CONCLUSION:

This natural-polymer-based hydrogel sustained-release system of Empagliflozin shows huge promise in terms of addressing the inherent challenges that are associated with the controlled delivery of drugs. A formulation like this may show stable plateau levels of released drugs for up to 24 hours. Consequently, a plasma drug profile would most likely adhere to the expected therapeutic drug objectives that will be observed in most chronic diseases like diabetes and other metabolic syndromes. This long-acting ability provides less frequent dosage but also allows consistent therapeutic drug levels, which improves compliance in patients and effectively manages chronic conditions. Almond and neem gums are two natural polymers that are highly useful in drug delivery applications. The biocompatibility, biodegradability, and nontoxicity associated with these materials make them an excellent choice for drug delivery systems and reduce the adverse impact on the environment due to synthetic options. Such properties include hydrophilicity and potential for crosslinking that enable strong, stable networks of hydrogels for sustained release and drug retention. This research discusses the range of applications this group of gums might find. However, their ability to control and change the drug release profile makes them uniquely versatile when tailored by the density of crosslinking or polymer composition. Such flexibility is different when creating specific customizable drug delivery systems that can be suited to nearly all therapeutic requirements. There are several possible avenues for further improving the formulation. The formulation could be tested against a range of production batches using advanced purification and processing techniques for natural gums. Standardizing the composition of natural gums can be challenging because variations from batch to batch pose a problem due to environmental effects on gum characteristics. More advanced purification and processing can ensure consistency in the gum composition and gel properties, leading to the reliable performance of the gum across production batches. Exploration of different crosslinking strategies will improve gel stability with or without significant loss in its bioactivity, thus retaining the goodness of both natural almonds and neem gums, of course, with respect to a compound derived from Neem against microorganisms.

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