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DESIGN AND EVALUATION OF CURCUMIN SMART BIOGELS LOADED WITH *TAPOICA SAGO* BIOPOLYMER FOR NOVEL DERMAL DELIVERY

Siddharth Singh* and N. V. Satheesh Madhav

Faculty of Pharmacy, DIT University, Mussoorie Diversion Road, Makkawala, P.O. Bhagwantpur, Dehradun- 248009, (Uttarakhand), India.

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***Corresponding Author**
Siddharth Singh
Faculty of Pharmacy, DIT University, Mussoorie Diversion Road, Makkawala, P.O. Bhagwantpur, Dehradun- 248009, (Uttarakhand), India.

ABSTRACT

The natural therapeutics products has been served for the treatment of various diseases from a very ancient time has been reported into the medical world. Curcumin has been documented with multiple biomedical applications like anti-tumor, anti-inflammatory, antiseptic, anti-aging, wound healing, etc. Wound healing is a multiple side process carried out by four overlapping subsequent phases such as, hemostasis, inflammation proliferation and remodeling. Platelets aggregation occurred due to hemostasis which results into clot formation. The *Tapoica sago* polymer extracted and characterized for presence of various functional group. The main aim of research was to formulate biogels for dermal delivery systems by using a biopolymer isolated from *Tapioca Sago* for exploring the curcumin potential in the wound healing process. Five biogels were prepared [NG1 to NG5] and loaded curcumin with other co-processing agents. All formulations were prepared between the ratio Curcumin: bio-polymer[1:1, 1:2, 1:3, 1:4, 1:5] and subjected to evaluation parameters like pH, conductivity, spreadability, viscosity, Primarily screening techniques for determining Particle size and *in-vitro* drug release studies and statistical analysis performed. The NG2 formulation was found to be best formulation having 6.6pH, 5517 cps viscosity, 7.5g.cm/s spreadibility, 0.1ms conductivity, and 78.76% drug release, T50% 4.28 h and T80% 24.38 h with R^2 value 0.9420 and higuchi matrix was best fit model followed the supercase II transport release mechanism. The conclusion was drawn that bio-polymer can be used as a stabilizer cum as retardant and also used in various other types of drug delivery

systems and curcumin loaded biogel formulations can be used for wound healing by using dermal route.

KEYWORDS: Curcumin; *Tapoica sago*; Biopolymer; Biogels; Wound healing; Dermal delivery; Drug vehicle.

1 INTRODUCTION

Curcumin, a multifunctional polyphenol compound produce by the plant *Curcuma longa* which belongs to the Zingiberaceae family. It is a bright yellow colored compound which shows anti-oxidant, anti-fungal, anti-tumor and anti-inflammatory properties. It is a lipophilic molecule which follows the diffusion process to permeates the cell membrane. Curcumin has been reported to obstruct the COX[cyclo-oxygenase] and lipo-oxygenase enzyme which responsible for the inflammation. Curcumin also shown anti-tumoral activity followed by the inhibition of COX-2 in colon cancer. It also has been observed that the process apoptosis, p53 activation and nuclear translocation induce by the curcumin in human neuroblastoma cells. It found that wound on skin caused by fractionated irradiation and carbon-dioxide lasering healed by the curcumin shown in animal's model. Curcumin also gets an approval by USFDA as "Generally Recognized As Safe".[1-4]

Biogels are three dimensional hydrogel network systems that composed of ionic or non-ionic nanoparticles and polymers formed by covalent linkages with biocompatible and biodegradable properties. These agents has tendency to deliver the drug beyond the physiological barriers as well as they are good carriers due to high stability. The different types of polymers like chitosan, poly (ethyleneimine), poly (N-isopropyl acrylamide), poly (vinyl alcohol), alginate, poly (ethylene oxide), poly (vinylpyrrolidone), and carbomers. It has been reported that curcumin loaded Biogels with particle size range 10-200nm shows various results like increased stability, improved anti-cancer effects, developed bioavailability, prolonged better life, increased treatment of melanoma and inhibited cancer cell growth in melanoma, breast cancer and in pancreatic cancer cells. Biogel has excellent ability for the delivery of drug into systemic circulation via multiple routes like oral, nasal, pulmonary, intraocular, topical followed by diverse features such as higher drug loading capacity, permeability, particle size, non-immunologic response, colloidal stability, high biocompatibility and bio-degradability, inert property, ability to cross blood brain barriers(BBB) and suitable for hydrophilic and hydrophobic drugs, etc.[5-7]

The biopolymer shows unique features due to its uniqueness of being pure, eco-friendly in nature, less cost, biocompatibility, bio-degradability, filmability, mucoadhesivity, retardability, acceptable for as a drug vehicle for sustained release dosage forms, etc.

Gaurav Aggarwal et al. reported the *Tapoica sago* biopolymer isolation by using di-methyl ketone non-solvent addition method and its various spectral analysis results such as IR spectroscopy which showed biopolymer stipulated multiple peaks which signifies the presence of various functional groups such as alkenes(3071.22cm^{-1}), aldehydes(1717.24cm^{1}), aromatics bending(1609.07cm^{-1}), esters(1348.05cm^{-1}) which responsible for bioretardant and drug delivery vehicle, and other various properties of biopolymer(figure 2), SEM signified the biopolymer morphology that was found irregular in shape with 100 µm size range(figure 3), DSC depicted the peak and peak height which was obtained at 117.21ºC and 19.7534mw(figure 4), NMR indicated the peaks identified disclose the presence of functional groups such as RO-CH_3(figure 5), MS showed the polymer nature and protein presence determined by large molecular weight which displayed in mass spectra(figure 6). Using of *Tapoica sago* biopolymer screening its filmability in bio-flexyfilms and evaluation parameters was reported.[8,9,12] Hence, the main aimed was to formulate and evaluate the *Tapioca sago* biopolymer loaded curcumin biogels effects in the wound healing process (figure 1).

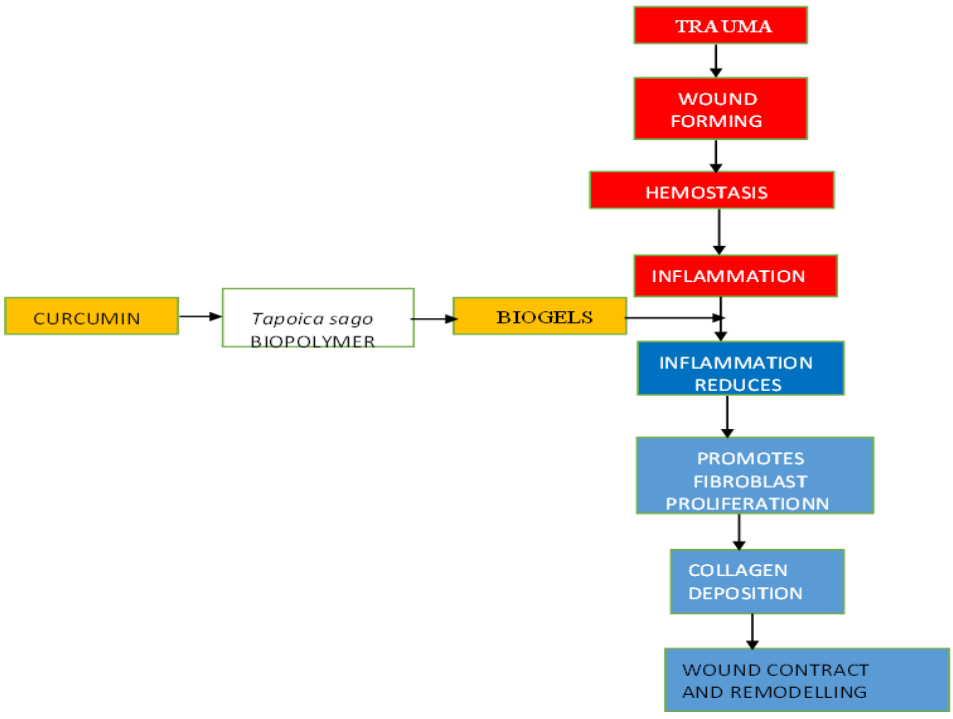

Figure 1: Sketch of effect of curcumin biogels in the wound healing process.

2 MATERIALS AND METHODS

2.1 Materials

Curcumin was provided as a gift sample by Indian Glycol Limited [Dehradun, Uttarakhand, India], Sago was procured from local market and other excipients like dextrose, starch, PVA, HPMC, Tween 80, sodium benzoate and distilled water were of highest purity and analytical grade and double distilled water was used from beginning to end of experimental work.

2.1 Isolation of Biopolymer from *Tapoica sago*

500gm of Tapioca sago procured into the powder form with the help of mixer grinder and the slurry was prepared by the addition of 600ml distilled water and passed through the muslin cloth. Optimized the quantity of filtrate and added the acetone in proportion of 1:2 to the filtrate. The mixture was refrigerated at 2-8ºC for 24 h and centrifuged continuously 15 min at 3500rpm for the isolation of biopolymer. The biopolymer was settle down at the bottom of mixture and supernatant was discard. The biopolymer obtained by naturally dried process until converted into powdered form for 24 h and passed through sieve 120. The biopolymer was stored for further use. The whole process repeated three times for optimization and percentage yield was determined and reported.[12]

2.2 Characterization of physical and chemical properties of isolated biopolymer

2.2.1 Physical properties like color, odor, melting point and solubility.

2.2.2 Chemical properties like test for presence of carbohydrates, proteins and starch.

2.3.2.1 Molish reagent test: 2ml solution of biopolymer was placed in a test tube and followed by 2 drop addition of molish reagent. The solution was transferred into the another test tube in which concentrated sulfuric acid was added and color was observed and reported.

2.3.2.2 Biuret test: 2ml of biopolymer solution was placed in a test tube and added 1ml of 1% sodium hydroxide solution followed by addition of 1% copper(II)sulphate solution drop wise. Then mixture allowed to stand for 5 min, color was observed and reported.

2.3.2.3 Test for presence of starch: 2ml of biopolymer solution was placed in a test tube and added 1 or 2 drops of iodine solution and color was observed and reported.

2.3.2.4 Test for presence of reducing sugars: 2ml of biopolymer solution was placed in a test tube and added 1ml fehling solution A and fehling solution B respectively. The test tube was heated at 60ºC, color was observed and reported.[9, 10, 11]

2.3 Drug- excipient interaction study

The interaction study between the drug and excipient performed by two different methods which is called as dry method and wet method respectively. The drug and excipient[biopolymer] was assorted together into the three different ratio such as 1:1, 1:3, 3:1 and allow to stand for 3 days at room temperature. The methanol was used for dilution of 3 different drug: excipient mixture and analyzed by ultraviolet spectrophotometric method.[10]

2.4 Standard curve development of Curcumin

10mg of curcumin was transfer into the 100ml volumetric flask which contain 30ml of buffer solution of pH 7.4 and diluted with distilled water (100µg/ml) up to the mark. Various concentrations like 2, 4, 6, 8, 10, 12, 14, 16, 18, 20 µg/ml were transfer into 10ml volumetric flask and diluted with distilled water and absorbance was determined at 421nm versus followed by solvent blank and results were recorded.

2.5 Preparation of Curcumin Biogel

The 10mg curcumin drug solution was prepared by 10ml of acetone and transferred into the 10mg *Tapoica sago* biomaterial solution followed by other various excipients like 500mg gelatin, 500mg dextrose, 500mg starch, 2.5ml glycerine, 10 mg Polyvinyl Alcohol, 10mg HPMC, 0.1ml Tween 80, 5 mg sodium benzoate and 15ml distilled water. The prepared heterogeneous solution was go through the sonication process for 45 min at room temperature. After the sonication process, the drug- biopolymer solution was incorporated into the gelatin solution with continuous stirring at 40ºC-50ºC for 10 min and was kept under at 2ºC-4ºC. the five formulations was prepared into five different ratio such as 1:1, 1:2, 1:3, 1:4 and 1:5 between curcumin and biopolymers respectively. the biogels was obtained, packed in well closed container and subjected to the various evaluation parameters and reported.

Table 1: Preparation formula table of Biogels with different ratios.

Formulations	**NG1**	**NG2**	**NG3**	**NG4**	**NG5**
Drug: biopolymer ratio	**1:1**	**1:2**	**1:3**	**1:4**	**1:5**
Curcumin(mg)	10	**10**	10	10	10
Tapoica sago biopolymer (mg)	10	**20**	30	40	50
Gelatin(mg)	500	**500**	500	500	500
Dextrose(mg)	500	**500**	500	500	500
Starch(mg)	500	**500**	500	500	500
Glycerine(ml)	2.5	**2.5**	2.5	2.5	2.5
Polyvinyl Alcohol(mg)	10	**10**	10	10	10

HPMC(mg)	10	**10**	10	10	10
Tween 80(ml)	0.1	**0.1**	0.1	0.1	0.1
Sodium benzoate(mg)	5	**5**	5	5	5
Water(ml)	15	**15**	15	15	15

2.6 Evaluation parameters for prepared biogels

2.6.1 Physical evaluation: the visual assessment like color, homogeneity and grittiness of formulated biogels was performed and reported.

2.6.2 Measurement of pH: 1gm biogel was dissolved into the 100ml of distilled water with continuously stirring and the glass electrode of calibrated digital type pH meter dipped into the biogel solution. the pH value was observed and reported.

2.6.3 Measurement of Viscosity: the Brookfield viscometer DVII model with spindle T95(T-bar spindle) to determine the viscosity reading of biogels formulations and reported.

2.6.4 Measurement of Spreadibility: 1gm formulated biogel was placed between the horizontal glass plates of size 20×20cm^2 and 125gm standardized weigh was placed to the upper plate for 5 min, diameter was measured and reported.

2.6.5 Measurement of conductivity: 1gm biogel was dissolved into the 100ml of distilled water with continuously stirring and the glass electrode of conductivity meter was dipped into the biogel solution and results was reported.

2.6.6 Primarily screening techniques for determining Particle range by using TDS meter: 1% biogel solution was prepared and then solution was measured its particle range by using TDS meter at micron and sub-nano level.

2.6.7 *In-vitro* drug release studies of formulated biogels: the release studies was done by with the help of modified M.S apparatus which carries 36 vials(receiver compartment) filled with buffer solution of 7.4 pH. This is thermostatically controlled compartment in which egg membrane tied between the donor compartment(filled with the biogel formulation) and receiver compartment at constant temperature 37ºC which maintain with the help of orbital shaker incubator. From the period of half-an-hour (30 min) to 24 hour (1440 min), sampling was performed and followed by replacement of fresh buffer solution every time and ultraviolet spectral analysis was performed for each sample.

2.6.8 Statistical Analysis

The statistical analysis was applied and data were subjected for evaluation through the one-way ANOVA performed by SPSS (Statistical Package for the Social Sciences) software and MS Excel. There is no significant difference among all the groups NG1 to NG5 at 5% level of significant.

3 RESULTS

3.1 *Tapoica sago* biopolymer isolation: The bio-polymer was isolated from Tapioca sago by simplified economic process by using di-methyl ketone non-solvent addition method and percentage yield was found to be 4.0± 0.25 w/w.

3.2 Physicochemical properties of isolated biopolymer: The extracted biopolymer from the *Tapoica sago* was shows as white color powdered texture with odorless in nature. The solubility of biopolymer was found into a methanol. It showed the positive result of molish reagent test showed purple color and biuret test showed violet color which reflect the presence of carbohydrates and proteins and at 260ºC reflects its color changing point(Table 2). The blue black color was observed in the starch test while insoluble red brick copper oxide precipitate was observed which showed the presence of reduced sugar.

Table 2: Physicochemical characterization of biopolymer.

Features	Description
Color	White
Odor	Odorless
Texture	Powder
Solubility	Methanol
Melting point	260ºC
Proteins	Present
Carbohydrates	Present

3.3 Drug- excipient interaction studies: the drug-excipient interaction studies between the excipients (isolated biopolymer of *Tapoica sago*) and curcumin drug discovered that, they did not interact with each other which confirmed by the no change observed in 421 ƛ max of UV method. The conclusion was drawn that biopolymer and drug are compatible with each other, both of them can be used safely for the biogel formulation.

3.4 Standard curve preparation: the curcumin calibrated curve at pH 7.4 showed linearity between the range 2 to 20 (2, 4, 6, 8, 10, 12, 14, 16, 18, 20) µg/ml (figure 7) displayed R^2(regression square value) to be 0.9921 and y = 0.091x – 0.0515.

3.5 Physical evaluation of biogels: the physical appearance of NG1-NG5 formulations was observed yellow in color and smooth in texture.

3.6 Evaluation of pH, viscosity, spreadibility, conductivity: the pH of curcumin loaded biogel NG1-NG5 formulations was found between the range 6.6-6.8 shown in figure 8, viscosity 5509-5593cps, spreadibility 7.2-8.2g.cm/s, conductivity 0.1-0.4ms (table3).

Table 3: Evaluation parameters of Biogels formulations.

Formulations	pH	Viscosity(cps)	Spreadibility(g.cm/s)	Conductivity(ms)
NG1	6.6	5509	7.2	0.1
NG2	**6.6**	**5517**	**7.5**	**0.1**
NG3	6.7	5548	7.3	0.4
NG4	6.7	5573	7.7	0.3
NG5	6.8	5593	8.2	0.4

3.7 Primarily screening techniques for determining Particle size by using TDS meter: the particle size of biogel formulations [NG1- NG5] was found between 245-299 micron sizes ranged particles and 1345- 1579 sub-nano size ranged particles shown in figure 9.

3.8 In-vitro drug release studies: the drug release % of formulations NG1 to NG5 was found between 78.76% to 91.34% which composed in different ratios 1:1, 1:2, 1:3, 1:4 and 1:5 of *Tapioca sago* biopolymer: curcumin shown in figure 10. T50% and T80% of formulations was depicted in figure 11 while kinetic release profile of biogels showed in table 4.

Table 4: Kinetic release of curcumin- *Tapioca sago* biogels.

Formulations	Best Fit model	Mechanism of release	R^2 value
NG1	Higuchi-Matrix	Supercase II transport	0.9400
NG2	**Higuchi-Matrix**	**Supercase II transport**	**0.9420**
NG3	Higuchi-Matrix	Anomalous Transport	0.9369
NG4	Higuchi-Matrix	Anomalous Transport	0.9426
NG5	Higuchi-Matrix	Anomalous Transport	0.9415

3.9 Statistical Analysis: the results of curcumin biogels formulations NG1-NG5 obtained from the one-way ANOVA depicted in figure 12.

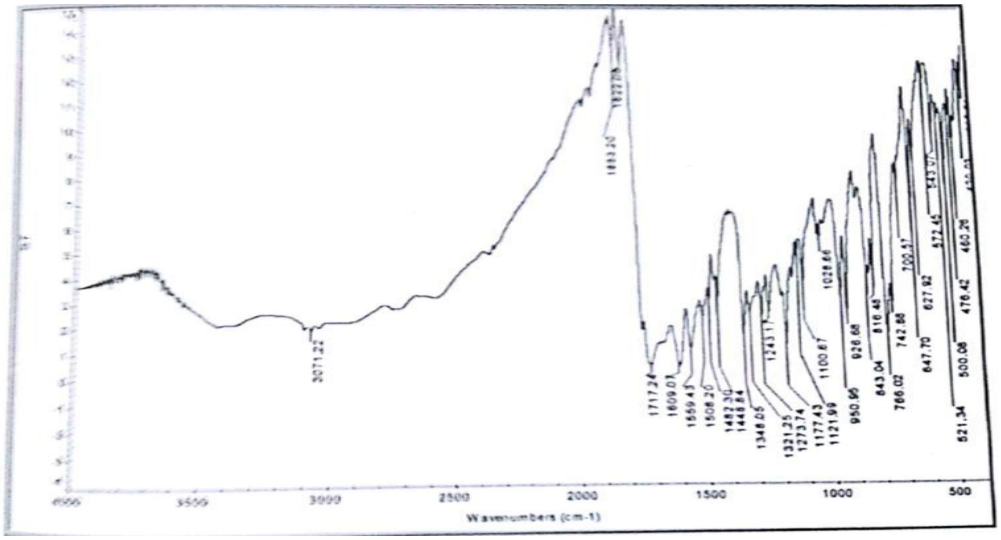

Figure 2: Biopolymer IR spectra.

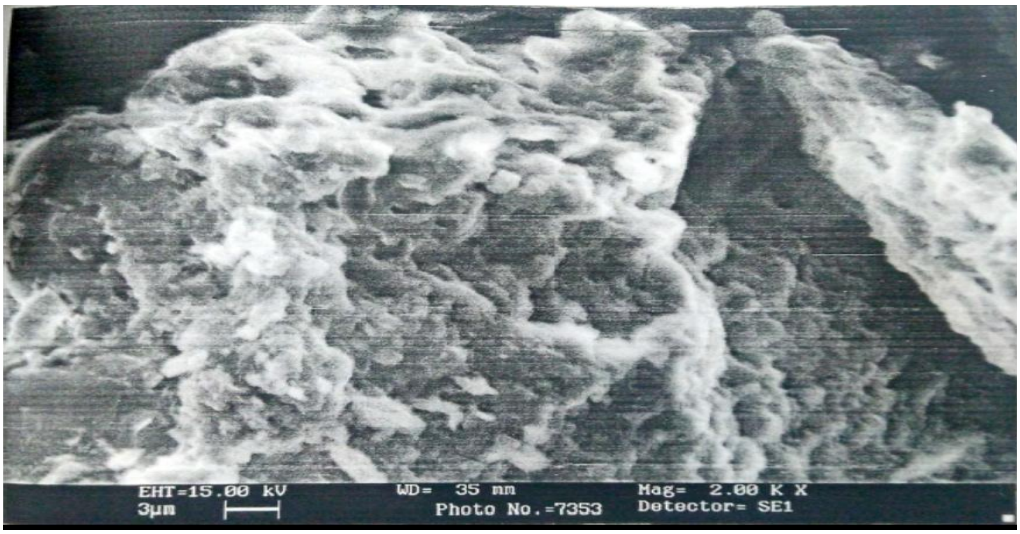

Figure 3: SEM of Biopolymer.

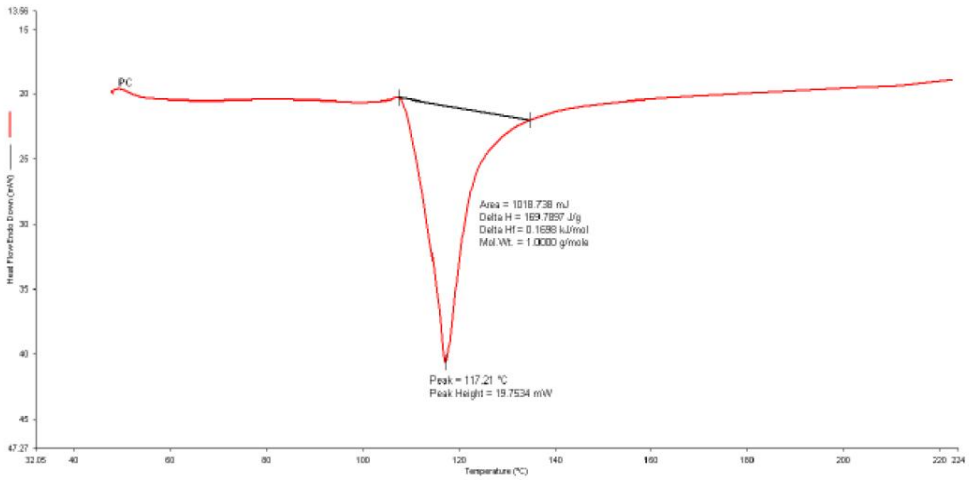

Figure 4: Differential scanning calorimetry of Biopolymer.

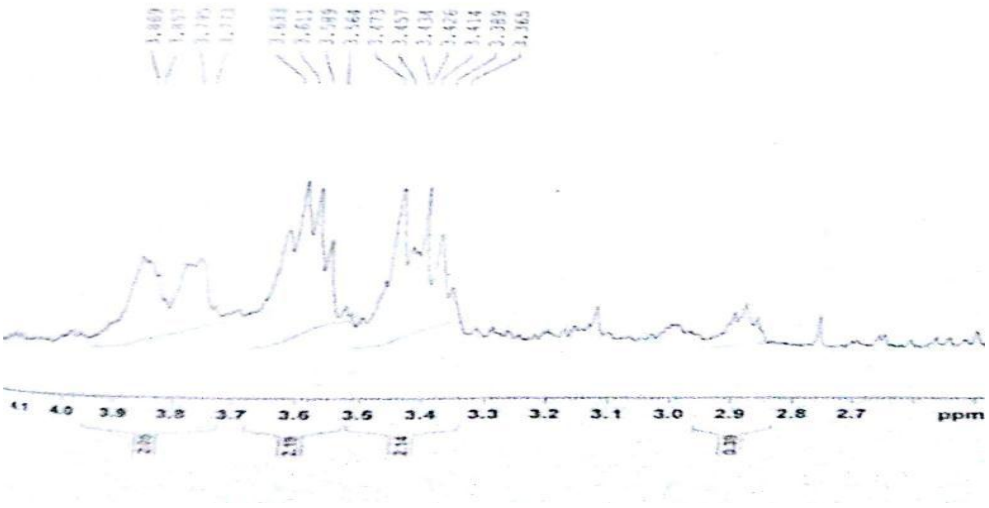

Figure 5: Biopolymer NMR spectra.

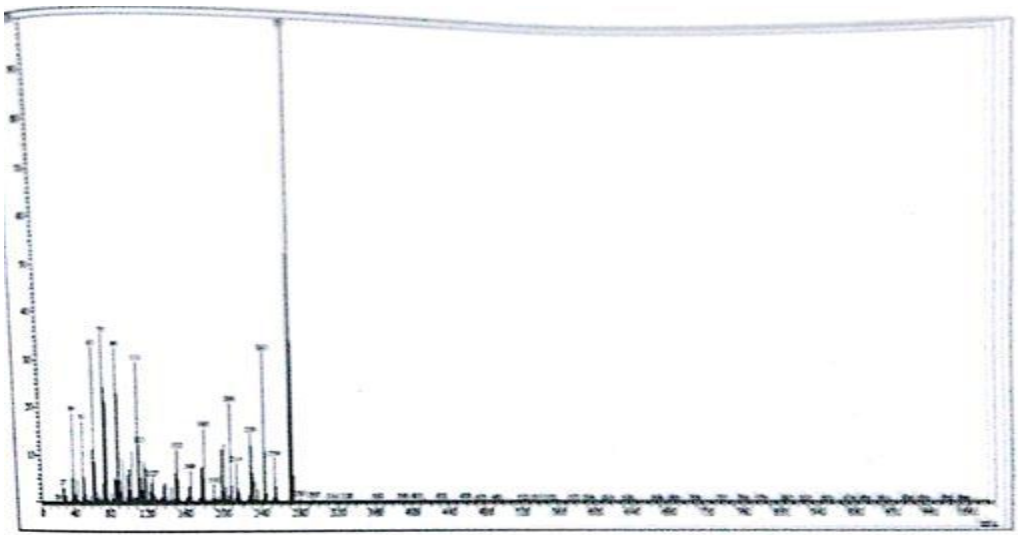

Figure 6: Biopolymer Mass spectra.

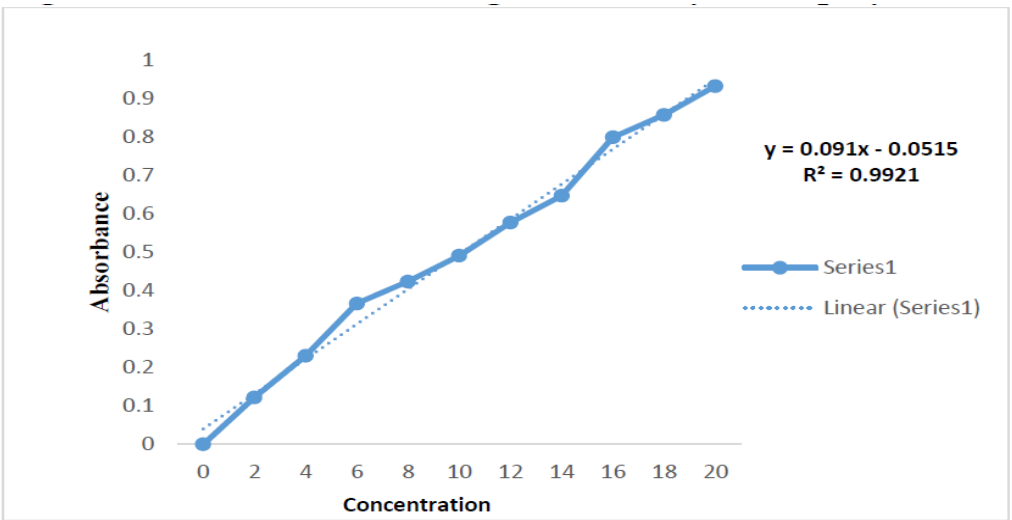

Figure 7: Curcumin standard Curve in Buffer pH7.4.

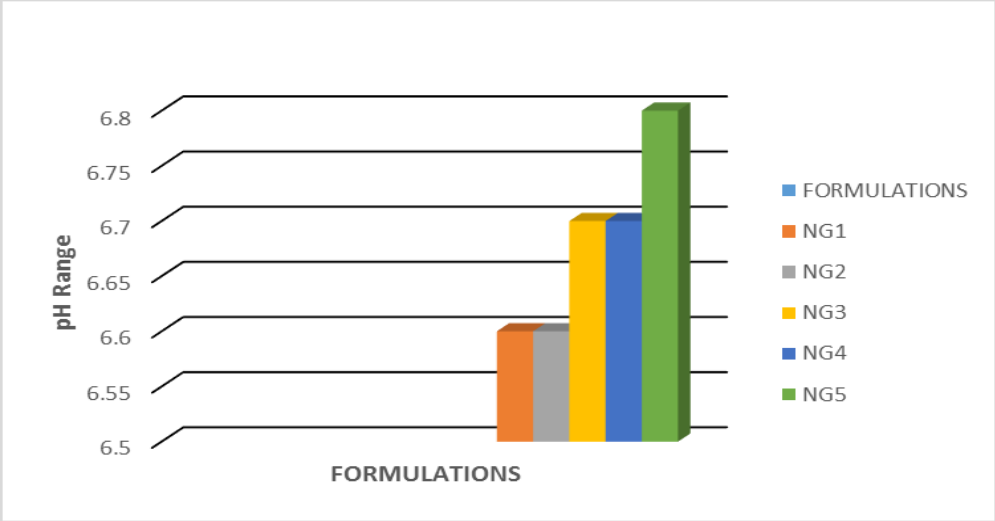

Figure 8: pH graph of Biogels formulations.

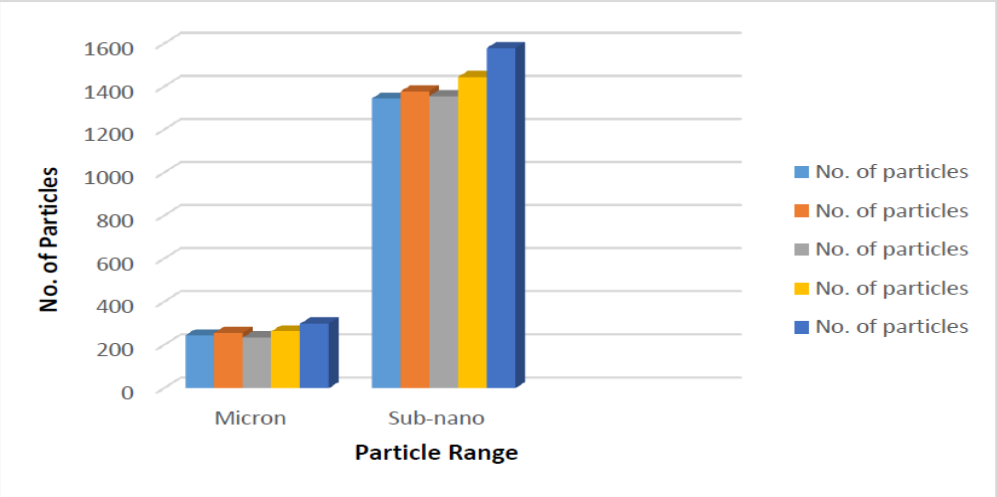

Figure 9: Particle size analysis of Biogels formulations.

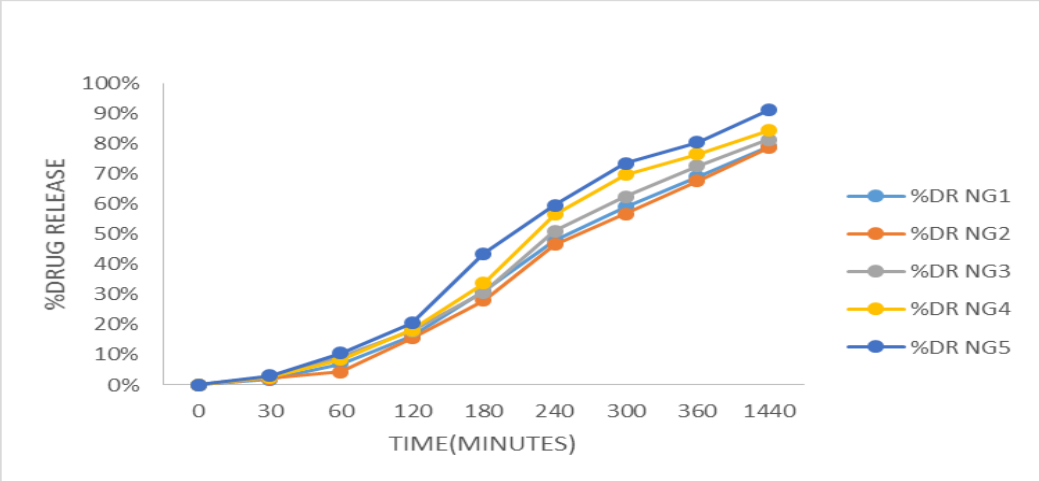

Figure 10: In-vitro drug release of Curcumin biogels loaded with *Tapoica sago* biopolymer by modified MS apparatus(NG1-NG5).

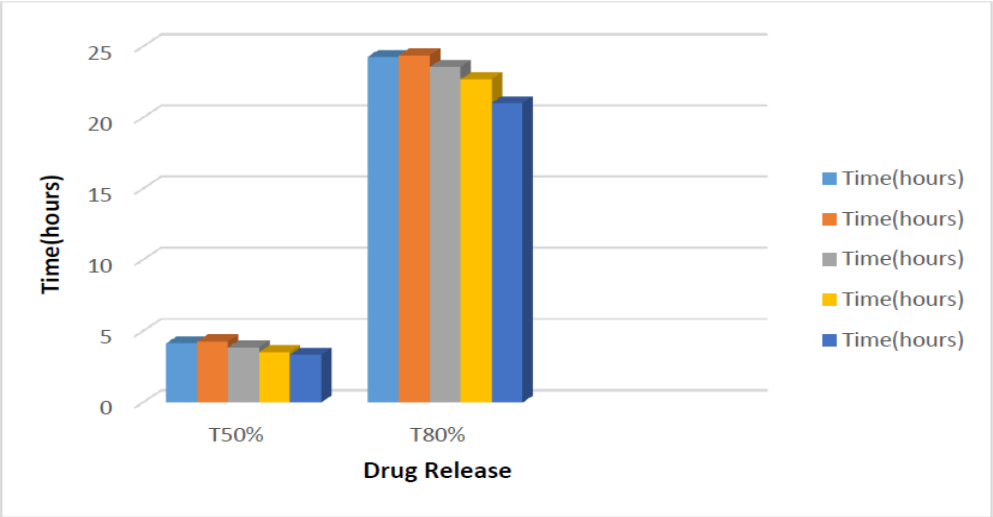

Figure 11: T50% and T80% of Curcumin- *Tapioca Sago* Biogels.

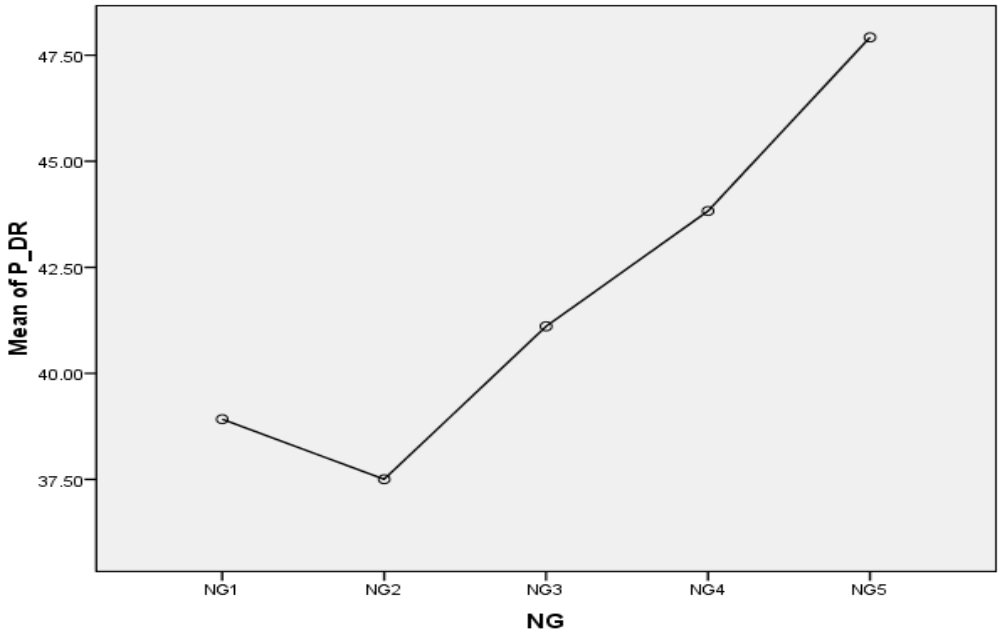

Figure 12: One-way ANOVA graph of curcumin biogels formulations.

4 DISCUSSION

There are several factor such as trauma, acne, burns, surgery, infection, diabetic skin wound, insect bite, etc. which caused skin wounds treated by curcumin into various different types of formulations such as liposomes, skin patches, hydrogel film, hyaluosomes.[13, 14] This research work explore the potential of curcumin delivery via dermal route by formulating suitable biogels using co-processing agents in optimized concentration. The *Tapioca sago* biopolymer was used a bio-excipient in designing of biogels because of multiple beneficial properties like biodegradability, non-toxic, biocompatibility, inertness, filmability, bio-stabilizers,

retardebility and bio-delivery agent. The multiple evaluation parameters of biopolymer and drug-excipient interaction studies were carried out and it was found that biopolymer were made up of proteins and carbohydrates and safely served as optimistic bio-excipient. Five formulations was designed into different ratios of drug: biopolymer NG1 [1:1], NG2 [1:2], NG3 [1:3], NG4 [1:4], NG5 [1:5] and evaluation parameters were carried out. The bio gels pH lies between 6.6-6.8, viscosity 5509-5593cps, spreadibility 7.2-8.2g.cm/s, conductivity 0.1-0.4ms, particle size between 245-299 micron and 1345- 1579 sub-nano level, T50% 3.34 to 4.15 h, T80% 21.02 to 24.27 h and % drug release 78.76%-91.34%. the one-way anova was applied in the evaluation parameters and *P*-value was found 0.964514. NG2 formulation (curcumin: *Tapoica sago* biopolymer in ratio 1:2) was found to be best formulation showed pH6.6, viscosity 5517cps, spreadibility 7.5g.cm/s, conductivity 0.1 and 78.76% drug release shown in figure 9 of comparative graph in-vitro drug release performed by modified MS apparatus for formulations (NG1-NG5). It also showed T50% 4.28 h and T80% 24.38 h shown in graph 10 and R^2 value 0.9420 with higuchi-matrix as best fit model followed the supercase II transport release mechanism confirmed by BITS software and can be used for wound healing. As biopolymer concentration increase, the release was retardant while viscosity and spreadibility was increase simultaneously but further increase in polymer concentration leads to increase drug release while decreasing the retardibility of the biogels. There was no significant change was found in ƛ max of curcumin and biopolymer which confirms as that biopolymer does not contain any reactive functional group and this shows that biopolymer was inert and natural. The study also reveals that biogels also enhances the solubility and bioavailability of poorly soluble drugs. As well as biopolymer served as a stabilizer cum as retardant into the biogel and can also be used into various formulations because of its multiple properties.

5 CONCLUSION

In this study, five different formulation (NG1-NG5) of curcumin biogels loaded with *Tapoica sago* biopolymer were formulated with other excipients for the wound healing. Based on results obtained from the evaluation parameters like T50%, T80%, pH, viscosity, spreadibility, conductivity, particle size screening and release kinetic profile, NG2 formulations (which composed of curcumin 10mg, *Tapoica sago* biopolymer 20mg, gelatin 500mg, starch 500mg, dextrose 500mg, glycerine 2.5ml, Poly vinyl alcohol 10mg, tween 80 0.1ml, HPMC 10mg, sodium benzoate 5mg and distilled water 15ml) was selected as the best formulation and can be served as bio-retardant for releasing the drug over an extended period

of 24 h. The study also reveal that *Tapioca sago* biopolymer served as bio-retardant for drug delivery in topical formulations.

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CONFLICTS OF INTEREST

Authors declared, there are no conflicts of interest related to this work.

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