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"DESIGN, DEVELOPMENT AND CHARACTERIZATION OF NANOGEL CONTAINING HERBAL DRUG".

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ABSTRACT:

The moto of the present study was to develop a herbal nanogel dermal formulation using ethanolic extract of ailanthus excelsa roxb stem bark so as to provide a natural herbal based antimicrobial activity over the skin disease. Further the formulation developed should be effective, easy to use ,non -irritant and cosmetically acceptable. Herbal medicines get Preferences over modern medicines due to minimum side effects and also healthier Option for the patients. Development of novel drug delivery system has a impact on disease Prevention, diagnosis, and treatments. This novel way have overcome the issues by Improving absorption of drugs, sustained release of drug, controlled release of drugs, By reducing toxicity of drugs etc.

KEYWORDS: Ailanthus excels roxb. stem bark extract, Antimicrobial activity, Nanoparticle, Nanogel

INTRODUCTION

Herbal medicine is often defined as "the therapeutic practices that are alive for many years, before the event and spread of recent medicines". This branch of other medicines that exploits medicinal plants for therapy is applied as herbal medicine which exploits medicinal plants for therapy is applied as herbal medicine which is mostly researched by many researchers. Herbal medicines from traditional herbs or natural herbs are logically considered as alternative medicines during this era to treat and cure most communicable diseases also as non-communicable diseases like cancer and diabetes.

Herbal medicines have played an important role in fixing the inspiration for current pharmacopoeia which is within the pharmaceutical market. Herbal medicines get preferences over modern medicines due to minimum side effects and also healthier option for the patients. Mostly 85% of Worlds population used herbal drugs to treat skin related diseases like viral, fungal, diabetic related issues, hypersensitive reactions etc. But in reality despite their appropriate pharmacological activity, they are less used in medicinal practices due to many reasons like solubility issues, bioavailability problems, high dose requirement etc. They can be used in day to day medicinal practices by using them in a novel way. And it results to reduces the dose of the herbs as a drug which is used for pharmacological activity, however easy accessibility and also cost effectiveness of these traditional medicines by making them more desirable as a alternative option for modern medicines .

Nanotechnology, a novel technique which having the broad scope for the drug delivery. Development of novel drug delivery system has a impact on disease prevention, diagnosis, and treatments. This novel way have overcome the issues by improving absorption of drugs, sustained release of drug, controlled release of drugs, by reducing toxicity of drugs etc. the application of nanotechnology to medicines has the development of nanoparticles which act as carriers can be loaded with drugs or genetic material which released in controlled or sustainable manner to specific target site. Many nanotechnological techniques available nowadays for drug delivery like nanoemulsions, nanosuspensions, nanotubes, and nanogels but despite other techniques nanogels are mostly available in market due to its advantages over other formulations. A nanoparticle which contains hydrogel with cross linked polymer network called as "Nanogel". A nanogel which is nanosized hydrogels which is crosslinked, small swollen particles which is made up from amphiphillic or hydrophilic polymer networks, these networks might be anionic or ionic. They acts as carrier for drug molecules and designed in the

way that can absorb active compounds by the formation of bimolecular interactions like hydrogen bonding, salt bonds etc. The main biological compound can be loaded into nanogels by allowing the interaction between matrix and active agent and these results more dispersed hydrophilic particles. This structure provides physical protection to active loaded molecule from degradation. And for that nanogels become the more flexible structure for controlled and sustained drug release to the target site.

MATERIAL AND METHOD

Experimental work

Authentication of plant

The dried stem bark of ailanthus excels roxb. Were collected from the rural area of pusad during the month of February. The plant was botanically authendicated by the botany department of BHMS college of pusad .The stem bark were dried in hot air oven .The dried leaves were subjected to size reduction by using grinder ,powder size was kept coarse .powder material was kept in an air tight plastic jar for further at room temperature.

Preparation of extract

Extract was prepare by continuous hot extraction using soxhlet apparatus with solvent ethanol . Each extraction was continued for 6-8 hrs. About 50 gm of accurately weighed homogenized powder was placed in thimble and solvent was poured on it .The extract was settle at bottom in the flask . The filtrate was transferred to a tarred petri-dish and evaporated to dryness on a hot plate . The residue was dried till its weight become constant ,cooled and weighed immediately.

The residue i.e.ethanol extract is then tested for its antimicrobial activity against gram positive (staphylococcus aureus) and gram negative (Escherichia coli) bacterial strain .varying concentrations from 1%, 2%, 3% upto 6% of extract were tested by cup and plate method.

Preformulation study of extract

Determination of maximum wavelength of ailanthus excelsa stem bark

The stem bark extract was taken and dissolved in distilled water to obtain a concentration range of 1000mcg/ml. The above solution is taken and scanned at a wavelength of 200-400nm to determine the wavelength at which maximum absorption take place.

Standard calibration curve of stem bark Extract

100mg of the stem bark extract powder was taken and dissolved in 100ml of buffer in order to obtain a concentration of 1mcg/ml.

Stock solution

From the above prepared standard stock solution 02, 04, 06, 8,10 and 12 ml stock solution is taken and it is diluted with 10ml of buffer. The resultant solution is scanned at 324nm and with the concentration and absorbance values obtained calibration curve was plotted.

Compatibility studies of Active ingredients and excipients

Stem bark extract and Excipents included in the formulation are taken and compatibility studies are carried out using FT-IR by KBR pellet technique.

FORMULATIONS:

As ethanol extract of ailanthus excels stem bark has shown optimum activity at 4% concentration ,different nanogel formulation containing 4 % concentration are formulated . nanogel containing constant concentration but different polymers are prepared.

Preparation of nanoparticles

Stem bark extract nanoparticles are prepared by sonication method using the probe magnetic stirrer equipment.

The nanogel is prepared from modified Emulsion Solvent Diffusion method. It is having 4 steps .

Step I in the first step Accurately weighed quantity of extract is dissolved in ethanol and propylene glycol with stirring (organic phase). Step II In the second step aqueous phase is prepared by using Carbopol -940 dissolved in water with continuous stirring and heat for a

20min in a magnetic stirring. And the drug phase (extract) is sonicated under ultrasonic bath Sonicator for 10min. Step III In this step drug phase (extract) is added drop by drop into aqueous phase during high speed homogenization for 30 min at 6000rpm to from emulsion. The emulsion is converted into nanodroplet by homogenizer results in o/w emulsion formed. Step IV In this step o/w emulsion is homogenized for 1 hour at 8000rpm and triethanolamine is added with continues .

Various excipients are changes in formulations with their concentration, procedure is same for all formulations batches.

Nanogel containing carbapol 940 (nanogel F1 and F2) Carbapol 940 was used here as a polymer . Concentration of extract is constant and excipients concentration are changes.

Table 01 Nanogel formulation containing carbapol 940 (Nanogel F 1 and F 2)

Sr.no.	Ingredients	Formulation f 1	Formulation f2
01	Extract	2 gm	2 gm
02	Carbapol 940	0.3 gm	0.5 gm
03	Ethanol	7.5 ml	10 ml
04	propylene glycol	2 ml	4 ml
05	Triethanolamine	2 ml	4 ml
06	Water	q.s.	q.s.

Nanogel containing carbapol with gaur gum (Nanogel F3 and F4)

Guar gum being a natural polymer with several intresting properties like biodegradability ,biosafety , biocompatibility and sustainability presents a potential case for use in pharmaceutical formulations and drug release studies.

Table 02 Nanogel containing carbapol with guar gum (f3 and f4)

Sr.No.	Ingredients	Formulation f3	Formulation f4
01	Extract	02 gm	02 gm
02	Carbapol 940	0.3	0.5 gm
03	Guar gum	0.2 gm	0.3 gm
04	Ethanol	7.5 ml	10 ml
05	Propylene glycol	2ml	4 ml
06	Triethanolamine	2 ml	4 ml
07	Water	q.s.	q.s.

Nanogel containing carbapol 940 with Eudragit and Tween 80 (nanogel F5 and F 6)

Eudragit s-100 (Polymer),and Tween 80 use as a stabilizer .

Table 03 Nanogel containing eudragit –100 and tween 80

Sr. No.	Ingredients	Formulation f5	Formulation f6
01	Extract	02 gm	2gm
02	Eudragit s-100	0.10gm	0.15 gm
03	Tween 80	0.1 ml	0.2 ml
04	Glycerin	03ml	05 ml
05	Carbapol 940	0.3gm	0.5 gm
06	Triethanolamine	02 ml	02 ml
07	Water	q.s.	q.s.

Nanogel containing Carbapol 934 with Eudragit RL-100 and poloxamer 407 (nanogel F7 and F8) Eudragit RL-100 and poloxamer 407 are use as astabilizer .

Extract and polymer are taken in ratio 1:10 as this ratio shows more stability and no flocculation or sedimentation is been observed ,also the required size to produce nanogel is obtained by this ratio.

Table 04 Nanogel containing Eudragit RL-100 and poloxamr 407

Sr. No.	Ingredients	Formulation F7	Formulation F8
01	Extract	02 gm	02 gm
02	Eudragit RL-100	05gm	10gm
03	Poloxamer 407	05 gm	10gm
04	Carbapol 934	0.5 gm	1 gm
05	Propylene glycol	05 ml	10ml
06	Glycerin	15 ml	20 ml
07	Triethanolamine	2 ml	4ml
08	Water	q.s.	q.s.

EVALUATION OF NANOGEL

a)Appearance

The prepared nanogel were inspected visually for clarity ,colour and the presence of any particles.

b) pH

The pH of the all nanogel was determined using digital pH meter .about 1 gm of nanogel was stirred in distilled water till a uniform suspension effected. The volume was made upto 50 ml and pH of the solution was measured.

c) Homogeneity

All developed nanogels were tested for homogeneity by visual inspection after the nanogels have been set in the container. They were tested for their appearance and presence of any aggregates.

d) Rheological properties

Rheological properties (study of deformation and flow of matter)are required in various pharmaceutical areas. some of the reasons for determining these properties are.

- It helps in understanding the physicochemical nature of vehicle and quality control of ingredients ,test formulations and final products,together with the manufacturing process such as mixing ,pumping and filling .
- It reflects the effects such as temperature and storage time on the products .
- It helps to acess a topical formulation with respect to the patient usage e.g. removal of the preparation from a jar or tube without spillage or spreadability and adherence to skin .
- Finally it helps to monitor the effects of vehicles consistency on the release of drug from the preparation and its subsequent percutaneous absorption .

e) Spreadability Spreadibility is determined by apparatus suggested by Mutimer. It consist of wooden block, which is provided by a pulley at one end. By this method, spreadibility is measured on the basis of “Slip” and “Drag”. A ground glass slide is fixed on this block. A sample of 0.1 g of nanogel under study is placed on this ground slide. The gel is fixed on the beach formula was pressed between two slides and a 1 kg weight is placed on the top of two slides and left for about 5 min to expel air and to provide a uniform film of the nanogel between two slides. Excess of the gel is scrapped from edges. The top plate is then subjected to pull the weight. With help of string attaches to the hook and the time required by top slide to cover the distance is noted. A shorter interval indicate better spreadibility, spreadability was calculated by using the formula,

$S=M.L/T,$

Where, S=spreadability, L=Length of glass slide, M=weight tied to upper slide, T=Time taken to separate the slides.

f) Excrudablity It is a usual empirical test to measure the force required to extrude the material from tube. The method applied for determination of applied shear in the region of the rheogram corresponding to a shear rate exceeding the yield value and exhibiting plug flow. The method adopted for evaluating nanogel formulation for extrudability is based upon the quantity in percentage of nanogel and nanogel extruded from lacquered aluminium collapsible tube on application of weight in grams required at least 0.5cm ribbon of nanogel in 10 sec. The measurement of extrudability of each formulation shows the triplicate and averages value is presented.

Extrudability = Applied weight to extrude the nanogel from tube (in gm)/ Area (in cm2).

g) Rheological Studies (viscosity)

Brookfield viscometer was used for the studies. First, the spindle was dipped into the nanogel till the notch on the spindle touched the nanogel surface. 3gm each of nanogel (Stability chamber and Room temperature) was used in the study. The spindle no.61, 63, 64 was selected based on viscosity of nanogel. The dial readings were taken at 50, 100, 150, 250 rpm and viscosity was measured.2,4,5,6,7 From the evaluation parameter performed for the all prototype batches, the result for the batch f- 6 was found to be satisfactory in all attributes and hence selected for trial batches.

h) Extract content

For the estimation of the extract in nanogel, extract was extracted from 1 gm of nanogel formulation with 50 ml of phosphate buffer 6.8 and mixture was filtered through membrane filter (pore size 0.45 µm). From this, 2 ml was pipette out and made upto 10 ml. The absorbance of the sample was determined spectrophotometrically at 276 nm. The concentration of extract was estimated from the calibration curve.

i) In vitro Release studies

The drug release from the formulation was determined by using the apparatus known as Franz Diffusion Cell, which consist of a cylindrical glass tube which was opened at both the ends. 1 gm of nanogel equivalent to 10 mg of extract was spread uniformly on the surface of celloulose nitrate membrane (previously soaked in medium for 24 hrs) and was fixed to the one end of tube. The whole assembly was fixed in such a way that the lower end of tube containing nanogel was just touches (1-2 mm deep) the surface of diffusion medium i.e. 100 ml of pH 6.8 phosphate buffer contained in 100 ml beaker. The assembly was placed on thermostatic hot plate with magnetic stirrer and maintained at temperature 37°±2° the contents were stirred using magnetic bar at 100 rpm for a period of 24 hrs, 1 ml of samples were withdrawn at different time intervals. This 1ml was diluted upto 10 ml of fresh phosphate buffer (pH 6.8) and sample were analyze at 276 nm in UV-Vis spectrometer for extract.

j) Skin irritation test

Test for irritation was performed on human volunteers. For each nanogel, 12 volunteers were selected and 1.0 g of formulated nanogel was applied on an area of 2 square inch to the back of hand. The volunteers were observed for lesions or irritation .

No irritation -0

Slight irritation -1

Irritation -2

k) Microbial Assay

All the nanogel formulations were assayed for their antibacterial activity against gram positive (staphylococcus aureus) and gram negative (Escherichia coli) . the assay was arried out by cup and plate method . zone of inhibition indicate the formulation that give better effect to cure antimicrobial activity.

l) Stability batches evaluation

The stability studies were carried out on optimized formulation. The samples were stored at 40oC±2oC and 75%±5% relative humidity for three months as per ICH guidelines. After 1, 2 and 3 months samples were withdrawn and tested for appearance, pH, particle size, drug content, spreadability, extrudability, viscosity.

RESULTS AND DISSCUSION

Microbiological assay of ailanthus excelsa stem bark

The ethanolic ailanthus excels stem bark extract was assayed to test its activity against gram positive (staphylococcus aureous) and gram negative (Escherichia coli) bacterial strain. The assay has shown that ,ethanolic extract of stem bark at 4% concentration has better results at 4%,5% and 6% extract shows same zone of inhibition.

FTIR compability studies:

The individual FTIR spectra of extract and polymer Carbopol-940 and Eudragit S-100,Eudragit RL-100 as well as a combination spectrum of the extract and polymer . It was found that the Extract was compatible with polymer in physical mixture.

Appearance and skin irritation

Carbapol 940 (Nanogel F1 and F2), Carbapol 940 with guar gum (Nanogel F3 and F4) ,Eudragit S-100 with tween 80 (Nanogel F5 and F6) and Eudragit RL-100 with poloxamer 407 (Nanogel F7and F8) were found to be clear even after one month period of stability testing . Eudragit S – 100 with Tween 80 have a better stability and all properties than others.

Spreadability

The spreadability data shows how easily the nanogel is spreadable .lesser the time taken for the top plate to cover a fixed distance of 7.2 cm,indicates that there is less friction between glass surface and nanogel ,hence it can be said that ,nanogel is easily spreadable on the skin . Among various nanogel studied nanogel F6 has better spreadability ,as of less consistency it took only few seconds for the plate to cover a distance of 7.2 cm . The spreadability values of all formulations are given in following table .

Preference Testing : The panel was asked to evaluate using the score system given previously .

From all above test carried out to check the spreadability of different formulations,it was found that the spreadability of formulations was in following order.

Nanogel F6 > Nanogel F5 > Nanogel F8 > Nanogel F7 > Nanogel F3 > Nanogel F4 > Nanogel F2 > Nanogel F1.

Though the nanogel F1 takes a less time than nanogel F2,Nanogel F4,Nanogel F3 to cover a distance of 7.2 cm .this formulation was accepted less for spreadability by panel members ascompared to nanogel f 2 ,nanogel f4,nanogel ,nanogel f3 . this formulations are not stable and they are slightly changes are occure during stability period. The nanogel F6 containing Eudragit s-100 with tween 80 and carbapol 940 has shown better acceptance than the other formulations.

d) Extrudability test

For good nanogel formulation ,it should excrude easily from the container. The weight required to excrude the nanogel from container of different formulation was given in table no

The extrudability of nanogel was found to be in following order.

Nanogel f1 < nanogel f2 < nanogel f4 < nanogel f3 < nanogel f5 < nanogel f8< nanogel f7 < nanogel f6.

Viscosity

Rheological investigations are basically concerned with the determination of the relationship between shear stress and shear rate. Viscosity is measured in poises. Softer nanogel are generally found to exhibit greater release among the various nanogel studied : carbapol 940 nanogel had lesser consistency index than the eudragit s-100 and tween 80 with carbpol 940 nanogles.viscosity of all nanogel formulations was observed under different shear rates.

Microbiological assay of nanogels

The nanogel has slightly highest zone of inhibition on gram negative bacterial strain (Escherichia coli) than gram positive .nanogel F2 and F4 has same zone of inhibition .Nanogel F7 shows medium zone of inhibition while nanogel F6 shows highest zone of inhibition .nanogel F1has shown the lowest zone of inhibition.

Extract content

The extract content was found to be 93.76 ±0.43%. The results indicate that process employed to prepare nanogel in this study was capable of producing formulation with uniform extract content.

% Extract release study % extract release graph it is conclude that the f6 formulation that is eudragit s-100 with tween 80 shows best results than other one.

In- vitro extract release after stability studies

There were no physical changes in appearance and flexibility .after subjecting formulation to the stability studies.

Table 05 Calibration curve of ailanthus excels roxb.stem bark extract

Sr.no.	Concentration µg/ml	Absorbance
01	2	0.0181
02	4	0.0362
03	6	0.0724
04	8	0.0981
05	10	0.1291
06	12	0.1591

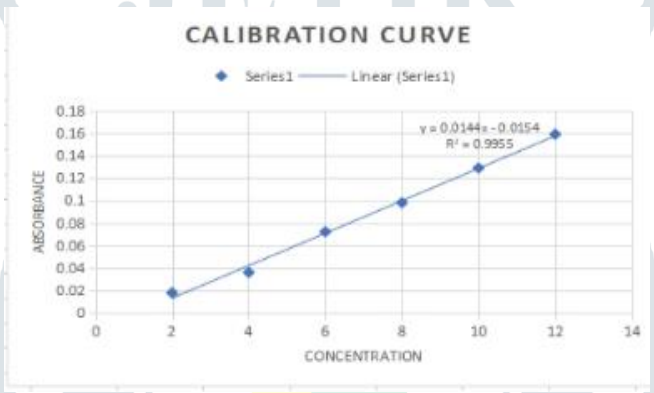

Fig. 01 Calibration curve of ailanthus excelsa stem bark extract

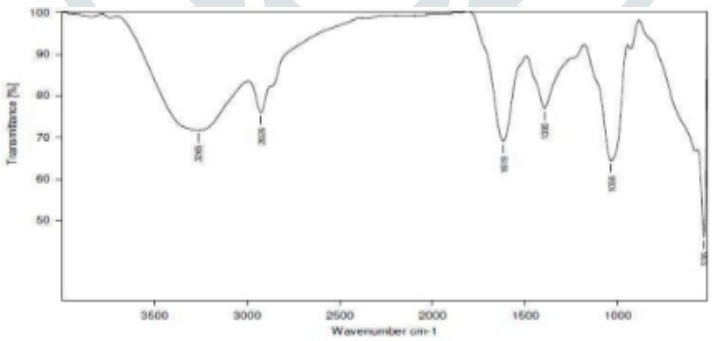

Fig . 02 FTIR Of Extract And Excipients

Table 06 Effect of ethanolic stem bark extract on gram positive bacteria (staphylococcus aureous)

Sr.No.	Concentration	Zone of inhibition(in mm)
01	1%	1.5
02	2%	1.9
03	3%	02
04	4%	2.9
05	5%	2.9
06	6%	2.9

07	Control	00

Table 07 Effect of ethanolic stem bark extract on gram negative bacteria (E.coli)

Sr.No	Concentration	Zone of inhibition(in mm)
01	1%	02
02	2%	2.3
03	3%	2.5
04	4%	03
05	5%	03
06	6%	03
07	Control	00

Table 08 Appearance and skin irritation score

Sr. No	Formulation	Appearance	Skin irritation score
1	F1and F2	Clear	0
2	F3and F4	Clear	0
3	F5and F6	Clear	0
4	F7and F8	Clear	0

Table 09 pH of nanogel

Sr. No.	Formulation	pH
1	F1	8.25
2	F2	8.19
3	F3	8.12
4	F4	8.02
5	F5	6.35
6	F6	6.59
7	F7	7.16
8	F8	7.25

Table 10 Spreadablity of nanogels

Sr. No.	Formulation	Spreadabilty (time in seconds)
1	F1	33
2	F2	29
3	F3	13
4	F4	12
5	F5	09
6	F6	05
7	F7	07
8	F8	08

Table 11 Extrusion pressure for nanogel formulations

Sr. No.	Formulation	Wt. Required (in gram)to excrude ribbon of 0.5 cm in 10 sec.
1	F1	223
2	F2	237
3	F3	253
4	F4	260
5	F5	269
6	F6	296
7	F7	289
8	F8	279

Table 12 Viscosity of nanogel

Sr. No.	Formulation	Viscosity in centipoise at 50 rpm
1	F1	8863
2	F2	8543
3	F3	8000
4	F4	9863
5	F5	9589
6	F6	9400
7	F7	9456
8	F8	9568

Table 13 Nanogel formulation and zone of inhibition on gram positive bacterial strain

Sr. No.	Formulation	Zone of inhibition (in mm)
1	F1	1.2
2	F2	2.8
3	F3	2.3
4	F4	2.8
5	F5	3.5
6	F6	3.9
7	F7	3.6
8	F8	3.3

Table 14 Nanogel formulation and zone of inhibition on gram negative bacterial strain

Sr. No.	Formulation	Zone of inhibition (in mm)
1	F1	01
2	F2	1.5
3	F3	1.7
4	F4	1.9
5	F5	3.5
6	F6	3.8
7	F7	2.2
8	F8	2.1

Table 15 % of extract (drug) release

TIME (min)	% OF EXTRACT (DRUG) RELEASE of BATCH							
	F1	F2	F3	F4	F5	F6	F7	F8
00	00	00	00	00	00	00	00	00
05	10.6071	25.0886	39.876	45.0543	11.9265	89.9865	85.6537	72.2564
10	14.9399	25.7654	40.6541	49.0854	14.9385	90.8765	86.9086	74.6547
15	15.3767	26.7654	42.7653	50.5536	16.4025	93.5674	88.7689	75.7654
20	15.9521	27.0547	46.9876	53.7654	17.9537	95.9876	89.5463	76.9865
25	19.0777	30.4567	47.9875	59.9837	19.2056	96.4532	90.8765	79.8763
30	2.0822	33.0987	49.9865	59.9837	22.6305	6.9876	91.0864	81.9876

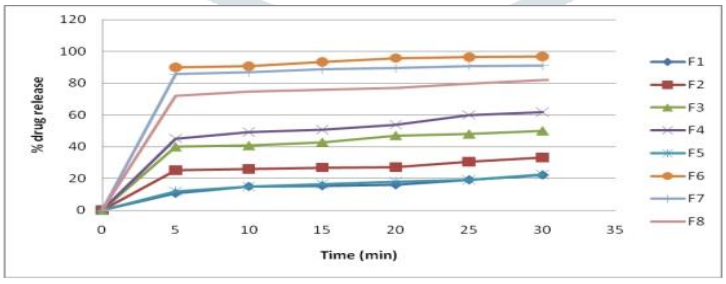

Fig. 3 Graph of % extract (drug) release verses time f1 to f8

Table 16 percent extract release of pure extract and its nanogel formulation after stability study

Sr.No.	Time (min.)	Percent extract release (%)	
		After stability(30) days pure extract	After stability (30) days f6 batch
01	0	0	0
02	5	59.1231	76.3456
03	10	60.5433	77.5432
04	15	61.9832	77.9876
05	20	63.9863	78.9876
06	25	65.9854	79.2135
07	30	67.9876	80.4536

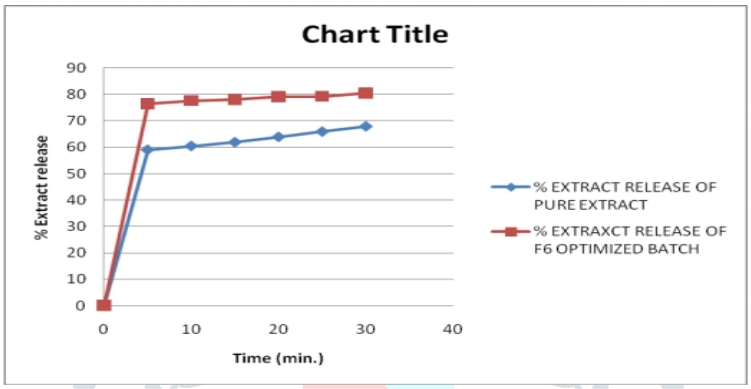

Fig. 24 .In vitro extract release profile of ailanthus excelsa stem bark extract and its nanogel formulations after stability study

SUMMARY & CONCLUSION

In the present study herbal nanogel formulation using ailanthus excelsa stem bark extract developed so as to provide a natural herbal based antimicrobial activity over the skin.

The material and methods used for the pharmacognostic studies of ailanthus excelsa roxb.extraction of stem bark, phytochemical screening using modern instrumental techniques, antimicrobial assay, experimental design, development and evaluation of formulations, stability and skin irritancy studies. The stem bark of plants under consideration were initially authenticated and Pharmacognostic and phytochemical analysis were done.

The extract was screen for antimicrobial activity against gram positive (staphylococcus aureous) and gram negative(Escherichia coli) bacterial strain.the nanogel shows best antimicrobial activity against (staphylococcus aureous).

The experimental design was done by using various polymers such as carbapol 940 guar gum eudragit-s -100 with tween 80, eudragit rl-100 with poloxamer 407 among that , carbopol 940 eudragit –s 100 with tween 80 and eudragit rl-100 with poloxamer 407 were selected as the independent variables and studied for experimental runs F1 to F9. The effect of the independent variable on the responses such as appearance, pH, spreadability, viscosity and extrudability were studied. F6 wich contain eudragit s-100 and tween 80 which gave promising resuts in all the aspects hence,this formulation has good future scope in pharmaceutical and cosmaceutical field in coming years.

Future Prospects:

The research work in the development of the nanogel containing herbal drug formulation studies need to be applied for patent and further studied clinically on humans, prior to approval by regulators for commercial adaptation by the pharmaceutical.

In vivo,in vitro corelationship studies.

Acknowledgement

I wish to place on record my sincere thanks to my family and friends and my well wisher.

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