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DESIGN AND DEVELOPMENT OF NANOGELS CONTAINING CARBAPOL AS POLYMER AND HYDROALCOHOLIC EXTRACT OF PTEROCARPUS MARSUPIUM AS HERBAL MEDICAMENT

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ABSTRACT

The aim of present work is to design *Pterocarpus marsupium* loaded nonogel for anti-inflammatory and to evaluate the nanogels by *in vitro* studies. Nanogels are swollen nanosized networks composed of hydrophilic or amphiphilic polymer chains that have attracted considerable attention as multifunctional polymer-based drug delivery systems. The gels were prepared by using extract of *pterocarpus marsupium*, carbapol 940, EDTA, ethanol, propylene glycol, methyl paraben, propyl paraben, triethalonamine and required quantity of water. The gels were prepared by nanogels from polymer precursors method, in this method extract was dissolved in propylene glycol and ethanol, in another phase carbopol was mixed in water and forms jelly like mixture, both mixture were mixed together and homogenized in high speed homogenizer: homogenize it up to formation of gel consistency: after homogenizing mixture was sonicated by using ultra sonicator for 20min. Evalution tests were performed by using various parameter prepared nanogel was stable, particle size was found to be in nano range. Prepared nanogels were stable, palatable, and acceptable and are compatible to consumers.

KEYWORDS: The aim of present work *Pterocarpus marsupium* compatible to consumers.

INTRODUCTION

Nanogels may be defined as nano-sized hydrogel systems which are highly cross linked systems in nature involving polymer systems which are either co-polymerised or monomers. Traditionally in the name of gels we have heard of semisolid formulations with three dimensional networks of organic systems encompassing fluids and drugs.[1] Nanogels are

typical formulations mainly of the size range of 100 nm, by varying solvent quality and branching the volume fraction can be altered variably to maintain a three dimensional structure. Nanogels are swollen nanosized networks composed of hydrophilic or amphiphilic polymer chains that have attracted considerable attention as multifunctional polymer-based drug delivery systems. They possess high water content, biocompatibility, and desirable mechanical properties. Colloidal particles ranging in size between 10 and 1000 nm are known as nanoparticles. They are manufactured from synthetic/natural polymers and ideally suited to optimize drug delivery and reduce toxicity. The successful implementation of nanoparticles for drug delivery depends on their ability to penetrate through several anatomical barriers, sustained release of their contents and their stability in the nanometer size. However, the scarcity of safe polymers with regulatory approval and their high cost have limited the wide spread application of nanoparticles to clinical medicine.[2]

The extract of *Pterocarpus marsupium* is acts as anti-inflammatory agent[3] and treatment of edema, antifungal etc. *Pterocarpus marsupium* has many uses[4] like it used as antidiabetic or also used in skin disease. Topical drug administration is a localized drug deliver topical drug administration is a localized drug delivery system anywhere in the body through ophthalmic, rectal, vaginal and skin as topical routes. Gels are external applications[5] having jelly like structure. Drugs are either dispersed mixed or embedded with help of gelling agent. Different type of gelling agents like natural, semisynthetic and synthetic has been used for preparation of gel. Even gels are spread over skin then the drug will released and can penetrate through layers of skin which require generally more time. On the other hand when the particle of gel are in nano size then there will be more absorption and significant bioavailability of drug which will produce quick effect in short time therefore it was our intension to disperse the powdered particle of extract of *Pterocarpus marsupium* with carbopol as gelling agent and by using homogenization technique.

MATERIALS AND METHODS

The extract was obtained by stem part of *Pterocarpus marsupium* [Vijayasar], which is available in institute.

Chemicals: Carbapol 940, Propylene glycol, Ethanol, Methyl paraben, Propyl paraben, EDTA, Triehalonamine were purchesed from LOBA Chemicals, Islampur through institute.

Method of Preparation

The gel was prepared by using dried extract of P*terocarpus marsupium* [Vijayasar]. The gel was prepared by using carbopol 940, methyl paraben, propyl paraben, triethalonamine, EDTA, and required quantity of water. This is divided into two parts. the quantity should be taken for various batches as given in formulation table. Required quantity of extract was dissolved in propylene glycol and ethanol. In another part required quantity of carbapol 940 was added in sufficient water and forms a carbopol jelly in that measured quantity of methyl paraben, propyl paraben and EDTA was added. Both phases are separately homogenized and sonicated by using ultrasonicator. After that phase 1 was added slowly in phase 2 with continue stirring by using homogenizer. Mixture was homogenized upto gel was formed [upto15 min] and sonicated it upto 20 min by using ultra sonicator.[5,6] The Nanodispersion of the extract was prepared by modified emulsification-diffusion method 100 mg of extract was weighed and dissolved in 10 ml ethylacetate containing polymer. This organic phase containing drug polymer mixture was added into the 30ml of aqueous phase containing Tween 80, with constant stirring at 5,000-10,000 rpm using High speed homogenizer. Addition of organic phase was done with the help of syringe positioned with needle directly into the aqueous stabilizer solution at the rate of 0.5 ml/min. The resulting dispersion was stirred for 6 min at 10,000-25,000 rpm and was subjected to the sonication for 5- 10 min. Then double distilled water was added slowly to the dispersion with subsequent stirring for1 hour to induce diffusion of organic solvent into the continuous phase and leading to the formation of nanodispersion. Gels of the Nanodispersion were prepared by dispersing a gel forming agent carbopol 940 in the Nanodispersion of extract by using high speed stirrer. The pH was adjusted to the 7.0 by using triethanolamine to form the gel and *Pterocarpus marsupium* enriched gels were stored at room temperature.

Evaluation of Nanogel

Appearance

The appeared gels were inspected usually for clarity, color, and presence of any particle. The test is important regarding patient compliance.[12,13]

Infrared Spectroscopy

FTIR spectra were recorded in KBr discs on a Shimadzu FTIR model 8000 under dry air at room temperature within the wave number range of 4,000–500 cm^{-1}.

Extrudability

For a good gel formulation, it should extrude easily from the container. This is also type of measurement of viscosity of formulations. In this test sample is extruded from the tube by usual procedure. An advantage of measurement using this method is that the sample remains literally undisturbed before making the measurement using this extrusion instrument which is suggested by Multimer, comparisons among the products can be made regarding the effect of filling under various stress conditions and extrusion under different conditions and extrusion under pressure closed collapsible tube under containing gel was passed firmly at end. When the cap was removed, gel extrudes until pressure was dissipates. The results for each formulation were recorded as extrusion pressure.

PH measurement

PH value of prepared nanogels were measured by using pH meter.[12-13]

Measurement of particle size of the formulation

The mean size and poly disparity index of the size distribution of the selected nanogels were determined by using Malvern Mastersizer 2000 MS (Malvern Instruments UK In shivaji University, Kolhapur). The mean particle size and size distribution were recorded.[12]

Determination of Zeta potential

The zeta potential of the selected formulation was measured by Beckman coulter (Beckman Coulter DelsaTM Nano Common) in Facility centre of Shivaji University, Kolhapur.[12,13]

Scanning electron microscopy (SEM)

Shape and surface morphology of the Nanogels prepared with optimized parameters was observed by scanning electron microscopy, at Facility centre of Shivaji University, Kolhapur.

Total drug content

A 0.5 gm of the prepared nanogel was diluted with 10 ml of ethyl acetate and filtered with a 0.45 µm filter. Total drug content was determined by UV spectrophotometry at 254nm using the formula.[12,13]

$$TDC = \frac{\text{Total amount of Nanogel} \times \text{Amount of drug in 0.5 gm Nanogel}}{\text{Amount of nanogel in gm W Initial drug} - \text{W Free drug}}$$

Stability

Short term Stability study of prepared formulation was carried out. Real time stability study was carried out by keeping the packs of formulations at 30 5^0C and 65% relative humidity and checking appearance, pH, exrudability, particle size, zeta potential at an interval of 03 and 06 months.

Spreadability

Spread ability of prepared formulations was carried out by using spreadability apparatus.

***In vitro* drug diffusion studies:** Dialysis membrane diffusion technique was used to study in-vitro diffusion of drug from the prepared nanogel formulations. The receptor medium used was freshly prepared phosphate buffer pH 7.5. Dialysis membrane (Molecular weight cut off- > 12, 000, Hi media) previously soaked overnight in the receptor medium was on the Franz's Diffusion cell assembly. 0.5 g of formulation was placed in the donor compartment and the assembly was kept on the multi station diffusion study apparatus at 37^0C ± 2^0C and stirred at 700 RPM. Aliquots of 0.5 ml were withdrawn at pre-determined time intervals (0.5, 1, 2, 3, 4, 5, 6, 8, and 24 hrs) and immediately replaced by same volume of the fresh medium. The aliquots were suitably diluted with the dissolution medium and analyzed by UV-Vis Spectrophotometer at 254 nm (λmax of crud extract in methanol). The data obtained from the *In vitro* diffusion studies were fitted to various kinetic equations to find out the mechanism of *Pterocarpus marsupium* release from the nanogels.

Swelling Behavior of Nanogels

The equilibrium swelling was performed to characterize the pH-responsive behavior of CMCh/PVA nanogels. To determine the equilibrium swelling behavior, freeze-dried CMCh/PVA (100 mg) was dispersed into distilled water (10 mL) and different buffer solutions of pH values of 4.00 and 9.00. The pH values of solutions were determined by the pH meter and the size of CMCh/PVA particle was measured using particle size analyzer Malvern Mastersizer 2000 MS (Malvern Instruments UK In shivaji University, Kolhapur) before and after swelling. The degree of swelling was defined as the volume ratio of CMCh/PVA after and before swelling. The measurements were made in triplicates using an analytical balance, and the error % was estimated to be 10%. The equilibrium degree of swelling of the gel was calculated as:

Swelling = We/Wd, where We is the weight of gel at the equilibrium and Wd is the weight of initial dry gel. Experiments were carried out till 120 min, and then all pieces were dried and re weighed again.

RESULTS AND DISCUSSION

Physical characterization: The formulation showed a clear nanogels with good consistency, transparency, extrudability and brown color It showed a uniform distribution particle and uniform dispersion with the polymer.

Drug content: The prepared formulations were analyzed for drug content. It was observed that the drug content in the prepared Nanogel was satisfactory and the drug was uniformly distributed in all the formulations. The percentage drug content is highest for formulation was about 63%.

PH measurement

PH of the prepared nanogel was found to be in neutral range which complies with the pH of the skin.

Average particle size

The particle size analysis revealed that, the Nanogel was in the nanometer range. The size of the nanoparticles was affected by the homogenization time and the concentration of carbopol 940. The size of the Nanogel containing *Pterocarpus marsopium* was found to be between 224.8nm to 557.6 nm.

Zeta Potential

The stability of the formulated Nanogel was evaluated by shivaji university, Kolhapur. measuring the zeta potential of the Nanogel (it shown between the desired range ±30 mV). Zeta potential of *Pterocapus marsupium* loaded formulations was in the range of 6.75 mV and Polydispersity index was found to be between 0.840 to 0.866.

Scanning electron microscopy (SEM)

Shape and surface morphology of the Nanogel prepared with optimized parameters was observed by scanning electron microscopy. The study shows that most of the Nanogel particles were moderately spherical in shape, the surface of the particle showed a characteristic smoothness, and the particle size was in the nanometric range, as depicted by

SEM. Some of the particles were found to be in clusters and mostly the overall formulation shows uniform dispersion of extract all over the gel as shown in the Figure18.

***Invitro* drug diffusion studies**

The mean (n = 3) cumulative amounts of drug diffuse through the egg membrane were performed for 12 hours, analyzed and their values are shown in Table 2. Among this five formulation F5 shows better release pattern as desired i.e., 69.90±3.64 for 12 hrs, due to good homogenization time, polymer concentration and uniform dispersibility of crude extract in the nanogel.

Stability

A stability study was conducted on batch F9 optimized formulation. The sample was withdrawn periodically after 30 days. Stability studies conducted for 90 days. After performing the stability study it was observed that at intermediate stability condition there was no significant change in final product when studied by applicable parameters.

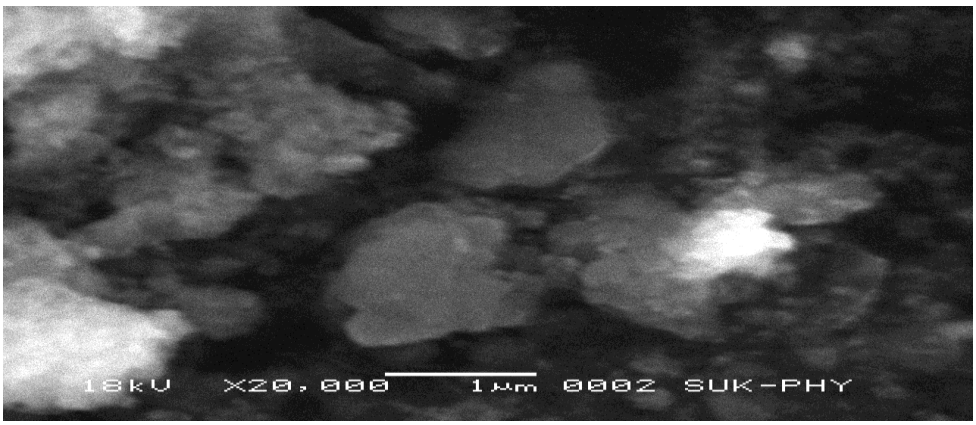


Figure 1: Scanning electron microscopy of nanogel.

Table 1: Composition of Nanogels.

Compostion (%)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Extract	1	1	1	1	1	1	1	1	1
Carbopol 940	0.5	1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5
Propyleneglycol	4	4	4	4	4	4	4	4	4
Ethanol	3	3	3	3	3	3	3	3	3
Methyl paraben	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Propyl paraben	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02
EDTA	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03
Triethanolamine	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3
Water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s	q.s

Table 2: PH, Spreadability and Drug content (%) measurement of nanogels.

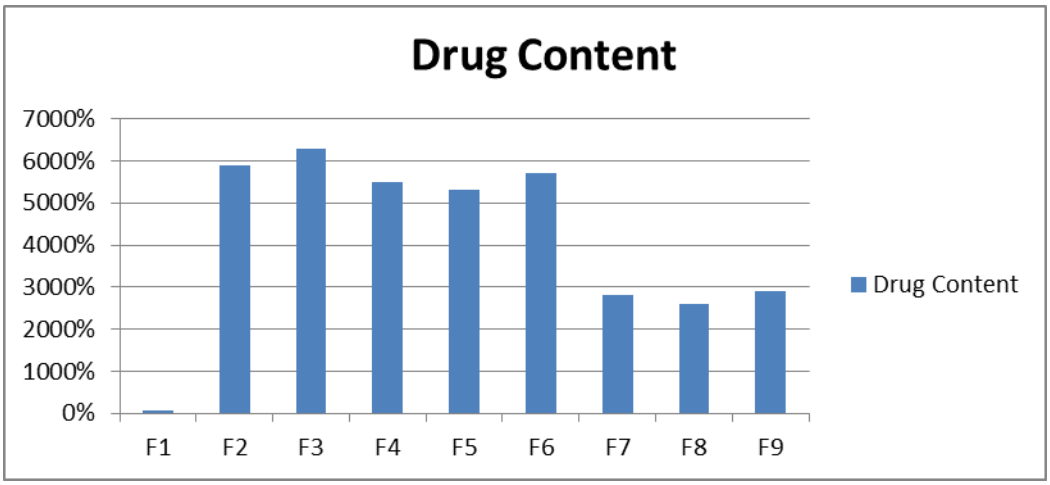
Batch	PH	Spreadability	Drug content (%)
F1	7.1	32	56
F2	7.2	30	59
F3	6.8	29	63
F4	7.25	28	55
F5	7.3	26	53
F6	7.2	29	57
F7	7.1	27	28
F8	6.9	26	26
F9	6.8	25	29

Table 3: *In vitro* drug diffusion studies for formulation F1-F9.

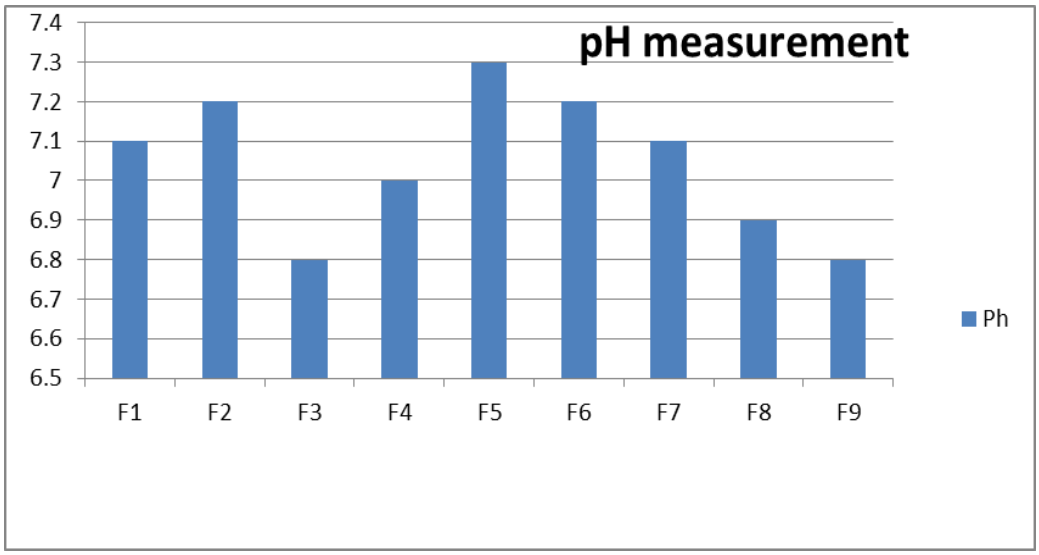
Time in hrs.	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	7.22± 0.05	6.63± 0.05	6.60± 0.10	9.10± 1.42	9.56± 1.66	8.56± 1.66	9.16± 1.66	8.56± 1.66	9.26± 1.66
2	12.35± 1.24	12.60± 1.24	9.54± 2.20	18.32± 2.44	15.73± 2.64	14.73± 2.64	14.73± 2.64	13.73± 2.64	15.63± 2.64
4	18.255± 2.20	18.69± 2.20	12.39± 2.40	28.96± 3.42	26.89± 3.66	24.89± 3.66	23.89± 3.66	22.89± 3.66	25.89± 3.66
6	28.32± 2.02	24.41± 2.02	21.14± 3.24	31.76± 3.98	38.58± 3.32	33.58± 3.32	33.58± 3.32	34.58± 3.32	36.58± 3.32
8	34.69± 2.10	28.22± 2.10	30.69± 2.62	51.11± 3.44	46.82± 3.44	42.82± 3.44	43.82± 3.44	42.82± 3.44	45.82± 3.44
12	52.32± 3.20	46.31± 3.20	41.66± 3.14	69.79± 3.22	67.90± 3.64	68.90± 3.64	65.90± 3.64	62.60± 3.64	69.90± 3.64

Table 4: Particle size and zeta potential data of nanogels.

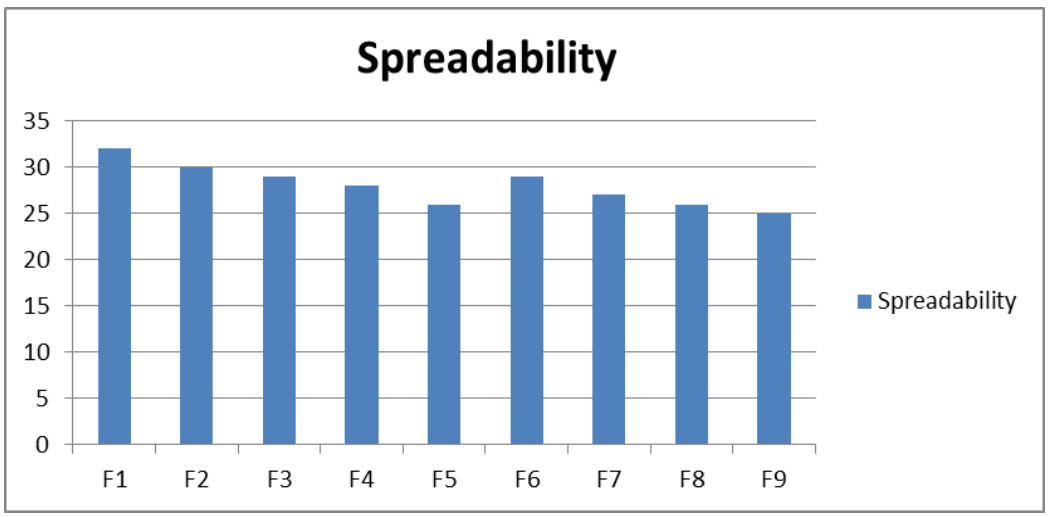
Batch	Appearance	Homogenisity	Exrudability	Particle size	Zeta potential	SEM
F1	Clear	Good	Good	440	7.9	Spherical
F2	Clear	Good	Good	450	7.8	Spherical
F3	Clear	Good	Good	500	7.55	Spherical
F4	Clear	Good	Good	600	8.3	Spherical
F5	Clear	Good	Good	396	8.1	Spherical
F6	Clear	Good	Good	780	6.1	Spherical
F7	Clear	Good	Good	689	8	Spherical
F8	Clear	Good	Good	456	6.75	Spherical
F9	Clear	Good	Good	780	6.5	Spherical



Graph 1: Graphical representation of drug content of nanogels.



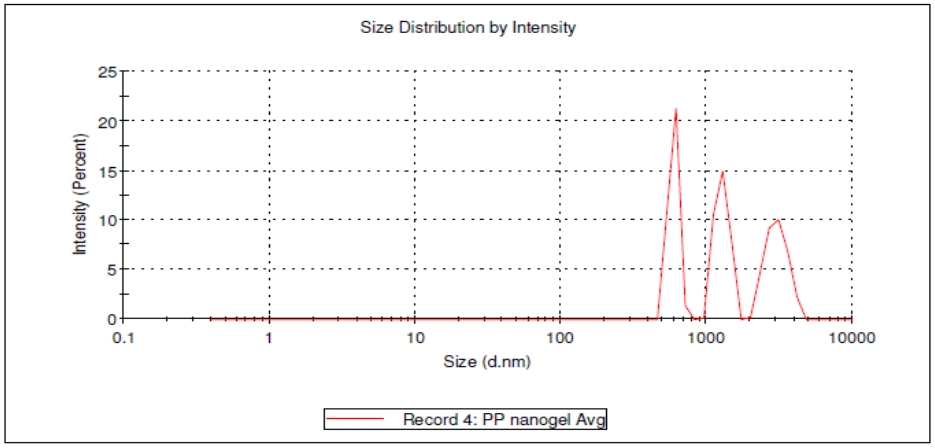
Graph 2: Graphical representation of pH measurement of nanogels.



Graph 3: Graphical representation of Spreadability of nanogel.

Results

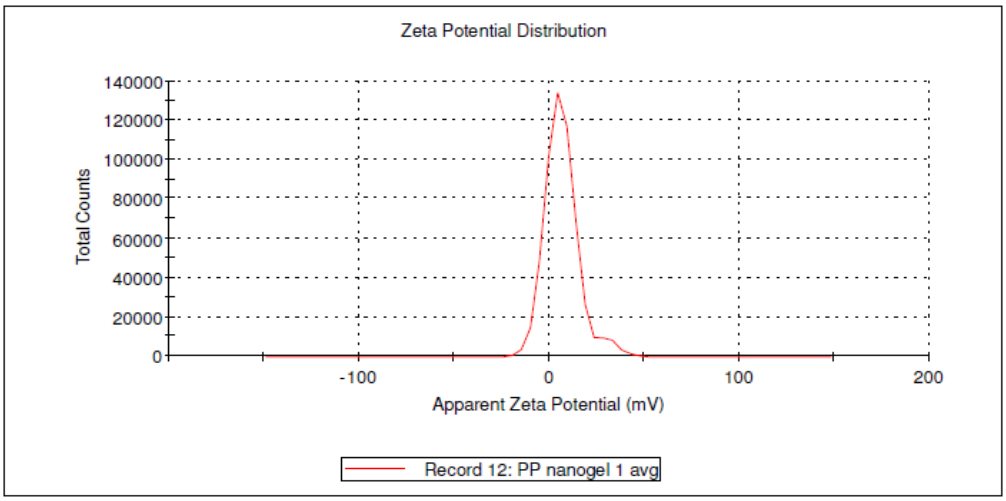
			Size (d.nm):	% Intensity:	St Dev (d.n...
Z-Average (d.nm):	4561	Peak 1:	3029	33.3	516.5
PdI:	0.826	Peak 2:	592.5	33.3	46.32
Intercept:	0.782	Peak 3:	1271	33.3	139.9
Result quality :	Refer to quality report				



Graph 4: Average particle size of nanogel.

Results

			Mean (mV)	Area (%)	St Dev (mV)
Zeta Potential (mV):	6.75	Peak 1:	6.72	100.0	9.25
Zeta Deviation (mV):	9.14	Peak 2:	26.8	4.0	3.91
Conductivity (mS/cm):	0.0136	Peak 3:	0.00	0.0	0.00
Result quality :	Good				



Graph 5: Zeta Potential of nanogels.

SUMMARY

Preformulation study was carried out total 09 Nanogels batches were prepared by trial and error method.

The gels were prepared by nanogels from polymer precursors method, in this method extract was dissolved in propylene glycol and ethanol, in another phase carbopol was mixed in water and forms jelly like mixture, both mixture were mixed together and homogenized in high speed homogenizer: homogenize it up to formation of gel consistency: after homogenizing mixture was sonicated by using ultra sonicator for 20min.

The prepared nanogels were characterized by different parameters like pH, spreadabilit, particle size analysis, zeta potential, scanning electron microscopy.

For the good stability of prepared nanogel formulations, the zeta potential of nanogels should be ranging between 3 mV-8mV.

The data obtained was analysed statistically.

CONCLUSION

From this study it was concluded that the polymers used in the formulation have great effect on various parameter. The novel nanogel from represents an effective and better carrier for topical preparation. The prepared nanogel showed stability over the study period. F8 batch is optimized when considered by applicable and critical parameters. The final product was viscous, transparent, jellylike structure, brownish, flavoured, palatable, acceptable, suitable, elegant and stable.

Future Plan

From present research work, the researchers have more scope to use blend of polymers and to formulate either herbal extract or marker compounds with polymers to get the final product of significant bioavailability.

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