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FORMULATION & EVALUATION OF NANOGEL FROM BENZOCAINE FOR GETTING ANALGESIC ACTIVITY

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ABSTRACT :

Nanogel fomulations enhance the delivery of drugs like benzocaine. It's a gel made up of tiny particles called nanogels that can efficiently release the drug. It's a promising technique for targeted drug delivery and can improved effectiveness. the abstract for a nanogel formulation using benzocaine could go something like this.

"In this study, we developed a nanogel formulation incorporating benzocaine, a local anesthetic. The nanogel was prepared using a biocompatible polymer, which formed a stable gel matrix. The nanogel exhibited excellent drug loading capacity and sustained release properties. In vitro experiments demonstrated enhanced permeation of benzocaine through the skin barrier compared to conventional gel formulations. Furthermore, in vivo studies on animal models showed prolonged anesthetic effect and reduced systemic absorption. These findings suggest that the nanogel formulation has great potential for improving the efficacy and safety of benzocaine delivery in local anesthesia."

Key Words : Benzocaine , Nanogel, Carbapol 934, Eudragit L-100.

1.Introduction:

Numerous analgesic formulations have been developed as a result of the search for an efficient pain management method. Because of its exceptional ability to numb specific locations, benzocaine, a common local anesthetic, has been a mainstay in pain management. However, the effectiveness of administration and duration of action are frequently issues with traditional benzocaine formulations.The development of delivery methods based on nanogel has become a viable strategy to address these issues. This study investigates the preparation of a benzocaine nanogel and its possible improvement in analgesic efficacy.[1-2]

Benzocaine is an ester local anesthetic commonly used for topical pain relief. It works by inhibiting voltage-gated sodium channels on the nerve membrane, preventing the propagation of pain signals. Despite its effectiveness, the limitations of benzocaine include its relatively short duration of action and potential for causing irrittion at the site of application.[3-4]

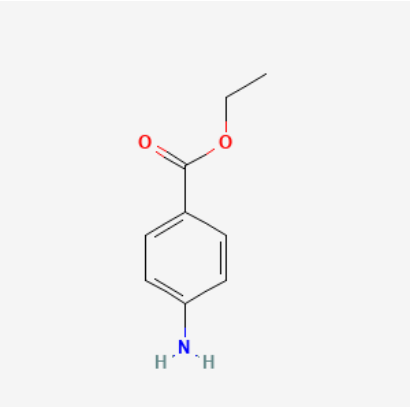

Fig 1: Benzocaine Structure

The advantages of hydrogels and nanoparticles are combined in nanogels, which are hydrogel particles at the nanoscale. Because of their biocompatibility, customizable size, and capacity to encapsulate a wide range of medications, they provide a significant degree of versatility in drug administration. The stability, bioavailability, and controlled release of medications that are encapsulated may all be improved by the application of nanogels..[5]

1.1.Advantages of Nanogel-Based Benzocaine Delivery:

1. Enhanced Stability: Benzocaine's shelf life is prolonged by encapsulation, which shield it from environmental deterioration.
2. Prolonged Release: Nanogels offer a regulated release mechanism that minimizes the need for frequent reapplication and permits a prolonged analgesic impac.
3. Lessened Irritation: Because nanogels are biocompatible, they can lessen the irritation that is frequently brought on by topical benzocaine treatments.
4. Targeted Delivery: Benzocaine can be administered more effectively at the site of pain if nanogels are designed to target particular tissues or cells. .[6-7]

1.2. Analgesic Activity- Mechanism of Action:

1. Pain Signal Inhibition: The nanogel formulation inhibits sodium channels in a manner akin to that of traditional benzocaine, but with a higher delivery efficiency.
2. Extended Duration: The analgesic action of the sustained release from nanogels guarantees a prolonged numbing and pain reduction for a prolonged duration.[8]

2. EXPERIMENTAL METHODS

2.1.Preformulation:

2.1.1.Determination of λmax of Benzocaine

10µg/ml standard (stock-C) solution of benzocaine was scanned in the range of 200-400nm using a UV-Visible Spectrophotometer and λmax was determined.[9-10]

2.1.2.Construction of Calibration curve of Benzocaine

Dilutions were prepared with Methanol to get concentrations of 2, 4, 6, 8,& 10µg/ml. The absorbance of these dilutions was measured at 235nm using UV-Visible Spectrophotometer. Methanol used as blank. The calibration curve was drawn by taking concentration on X-axis and absorbance on Y-axis.[11-12]

2.1.3.Drug-excipient compatibility studies

The Drug-excipient studies are done to study any possible interaction between the drug and excipients. FTIR spectrum of both pure drug and drug with excipients were taken and compared. The excipients should be compatible with the drug to formulate a nanogel.[13-15]

2.1.4.Determination of melting point

Place the sample in a capillary tube. Insert the capillary tube into the melting point apparatus. Rapidly heat the sample to a set temperature. Decrease the speed of the temperature increase to observe when the sample melts.[16-17]

2.2.Method of Preparation : Emulsion Solvent Diffusion Method

The Emulsion-solvent diffusion method was utilized in the formulation of the benzocaine nanogel. Glycerol is mixed with an accurately weighed quantity of drug, polymer Eudragit L-100, and stabilizer Tween-80. aqueous phase that was prepared with Carbopol-934 dissolved in water and heated while stirring continuously. Using an ultrasonic bath sonicator, these drug-containing phases are sonicated. During homogenization, the drug phase is gradually introduced drop by drop into the aqueous phase to create an emulsion. The homogenizer transformed the emulsion into nanodroplets, creating an O/W emulsion. For an hour, homogenization was maintained. Triethanolamine was added to create the gel while the nanogel was continuously stirred. At maximum speed, batches A1, A2, and A3 were made. However, using a homogenizer, prototype batches B1, B2, B3, and C1, C2, and C3 were made at various rpms, respectively. As shown in Table 1,2 & 3.

2.3.Batch Formulation:

2.3.1.Batch A

Table No 1: Batch Formulation Batch A

Composition	A-1	A-2	A-3
Drug(mg)	150	150	150
Eudragit-L-100(g)	0.23	0.30	0.37
Tween 80(ml)	0.15	0.45	0.75
Glycerol (ml)	7.5	1.5	22.5
Carbapol 934 (g)	0.75	0.15	0.45
Water (ml)	105	45	75
Triethanolamine (ml)	3	4.5	6

2.3.2.Batch B

Table No 2: Batch Formulation Batch B

Composition	B-1	B-2	B-3
Drug(mg)	150	150	150
Eudragit-L-100(g)	0.22	0.22	0.22
Tween 80(ml)	0.15	0.15	0.15
Glycerol (ml)	3.75	7.5	7.5
Carbapol 934 (g)	0.075	0.15	0.15
Water (ml)	22.5	45	45
Triethanolamine (ml)	1.5	3	3

2.3.3.Batch C

Table No 3 : Batch Formulation Batch C

Composition	C-1	C-2	C-3
Drug(mg)	150	150	150
Eudragit-L-100(g)	0.22	0.22	0.22
Tween 80(ml)	0.15	0.15	0.15
Glycerol (ml)	7.5	7.5	7.5
Carbapol 934 (g)	0.15	0.15	0.15
Water (ml)	45	45	45
Triethanolamine (ml)	3	3	3

2.4.Evaluation :

2.4.1.Physical characteristics:

The prepared nanogel formulations were inspected visually for their color. Appearance and consistency. tells about the physical characteristics.

2.4.2.pH determination:

The pH values of 1% aqueous solutions of the prepared nanogels were measured by a pH meter (Digital pH meter). Refer Table no 6.

2.4.3.Viscosity study:

The viscosity of the formulated batches was determined using a Brookfield viscometer with spindle 64 at 10 rpm. The assembly was connected to a thermostatically controlled circulating water bath maintained at 25˚C. The formulation whose viscosity was determined wasadded to a beaker covered with a thermostatic jacket. The spindle was allowed to move freshly into the nanogel and the reading was noted. The Table no 4 tells about the viscosities of the four formulations.

2.4.4.Measurement of spreadability:

Using two slides (5 cm2), the spreadability of the Nanogel was measured. Every batch of 0.5 g topical Nanogel was put between two slides and left for 1 min. The diameter of the topical nanogel spread circle was measured and compared witheach other.

2.4.5.Extrudability study:

After gels were set in the container the formulations were filled in the collapsible tube. The extrudability of the formulation was determined in terms of weight in grams required to extrude a 0.5 cm ribbon gel in 10 seconds.[18-19]

2.4.6. Drug content

After weighing and dissolving 1 g of Nano gel in 100 mL of methanol, it was sonicated for 15 minutes. After passing the solution through Whitman filter paper, the filtrate was used to dilute methanol. The drug substance and UV visible spectroscopy were used to measure the aliquot that was scanned at 292 nm wavelengths.[20]

2.4.7.Measurement of particle size of formulation

The Malvern Mastersizer 2000 MS was utilized to ascertain the average size of the chosen nanogels. It was noted what the average particle size .

2.4.8.In vitro Release studies

The device known as the Franz Diffusion Cell, which consists of a cylindrical glass tube that was opened at both ends, was used to measure the drug release from the formulation. After the cellophane membrane had been soaked in medium for 24 hours, 1 gm of gel, or 10 mg of benzocaine, was evenly distributed on its surface and attached to one end of the tube. The entire structure was fastened so that the gel-filled tube's lower end barely touched (1-2 mm deep) the surface of the diffusion medium, which was 100 ml of pH 6.8 phosphate buffer in a 100 ml beaker. The assembly was kept at a temperature of 37°±2° with a magnetic stirrer on a thermostatic hot plate. were withdrawn at different time intervals. This 5 ml was diluted upto 10 ml of fresh phosphate buffer (pH 6.8) and sample were analyze at 276 nm in UV-Vis spectrometer for Benzocaine.

2.4.9.Skin irritation test:

A human volunteer population was used to test for irritation. Four volunteers were chosen for each gel, and 1.0 g of the prepared gel was applied to the back of the hand in a 2 square inch area. We checked the volunteers for wounds or irritation.

2.4.10.Stability batch evaluation

The optimized for-mulation was used for the stability investigations. In accordance with ICH guidelines, the samples were kept for three months at 40oC±2oC and 75%±5% relative humidity. Samples were taken after 1, 2, and 3 months, and their appearance, pH, particle size, drug content, spreadability, extrudability, and viscosity were all examined. Data on the optimized formulation's stability. Evaluation parameters for appearance, homogeneity, particle size measurement, pH measurement, drug entrapment efficiency, drug content, in vitro drug release, skin irritation study, spreadibility, and extrudability were carried out for the trial batches (B and C) and the prototype batch (A) mentioned above.[21]

3.RESULTS AND DISSCUSIONS

3.1.UV Spectroscopy

After studying the UV spectra of Benzocaine it was found that drug shows absorbances at 234 to292 nm but maximum absorbance was at 292nm when solution is prepared in distilled water. So, 292nm was considered as λmax. UV spectra Benzocaine is shown in Figure 2.

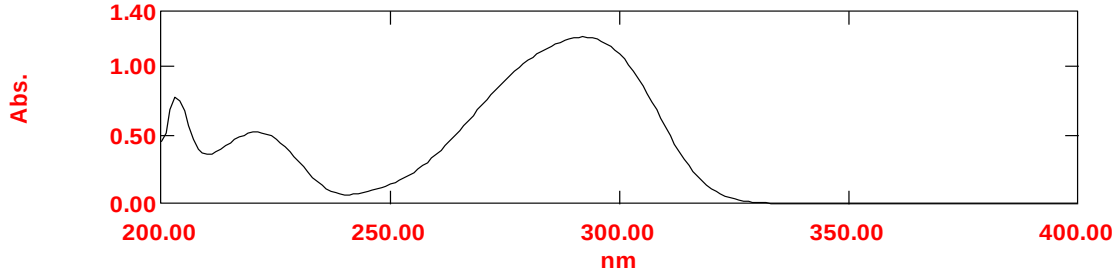

Fig 2: UV Spectra Of Benzocaine

3.2.Calibration curve of Benzocaine

The calibration curve for Benzocaine in Methanol is shown in Figure 3 and its observation values in the graph of absorbance vs. concentration was found to be linear in the concentration range of 4-24 µg/ml at 292 nm. The R2 of the calibration curve was found to be 0.9943.

Table No.4: Calibration curve of Benzocaine

Concentration	Absorbance
0	0
1	0.2518
2	0.4361
3	0.6616
4	0.8317
5	0.9894

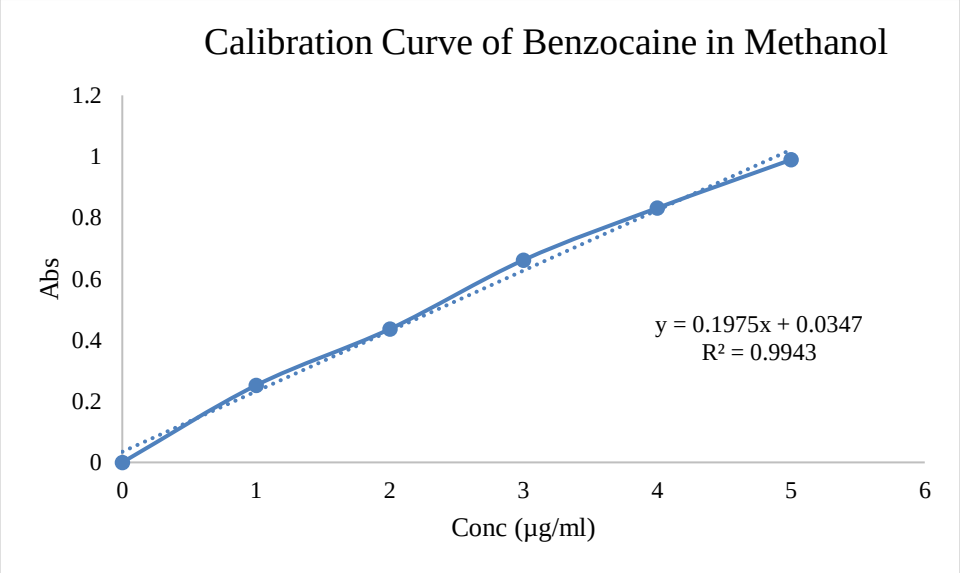

Fig 3: Calibration Curve Of Benzocaine

3.3.FTIR Spectroscopy

The FTIR spectrum for is shown in Figure and in Benzocaine interpretation of FTIR spectra is given in Table FTIR spectrum of drug sample showed all the peaks corresponding to the functional groups present in the structure of Benzocaine. From FTIR spectrum it was concluded that the drug sample was in pure form. shown in figure 4&5.

Fig 4: FTIR of Benzocaine

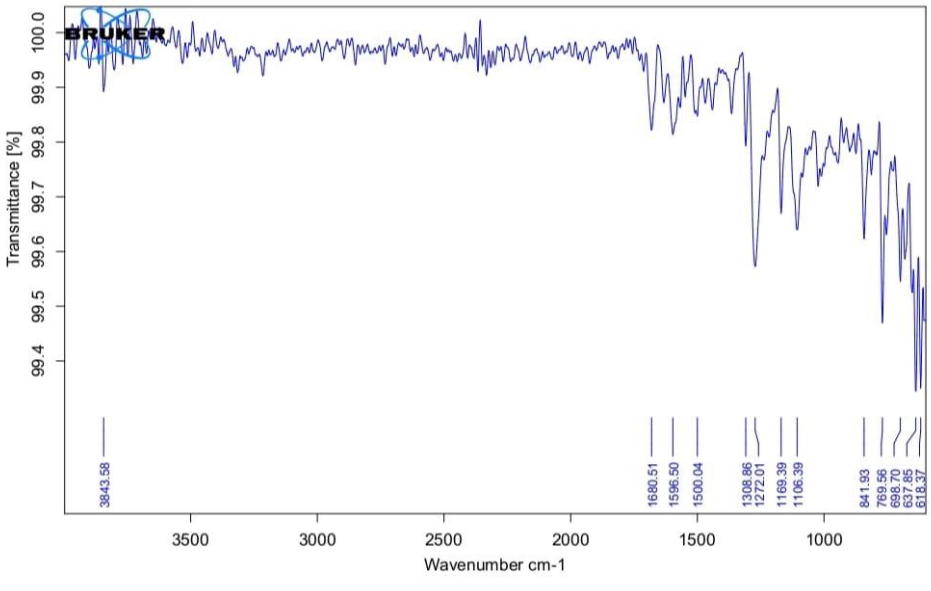

Table No.5: Functional Group Present in Drug FTIR

Functional Group	Standard	Observation(cm-1)
NH2	3500-3100	3450-3200
Aromatic C-H	3100-300	2983
Carbonyl	1900-1600	1679
Ketone	1300-1230	1272
C=O	692	770-700

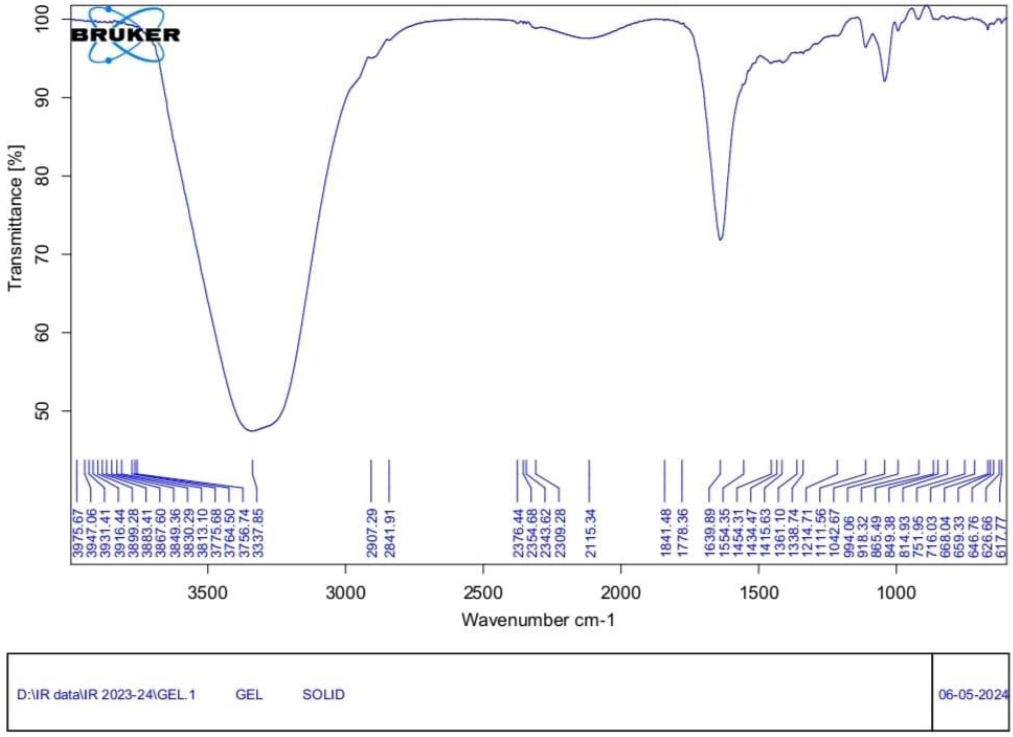

Fig 5 : FTIR Of Benzocaine with Excipients

Table No 6. Functional Group Present in Drug FTIR

Functional Group	**Standard (cm-1)**	**Observation (cm-1)**
N-H	3500-3000	3337.85
C-C	1600-1585	1639.89
C-Cl	850 -550	865.49

3.4. Melting Point

Melting point of the Benzocaine is 89 – 92 ^{0}C and Observed Melting of Purchased Benzocaine Is 89 ^{0}C.

3.5. Trial Batches Evaluation Results

3.5.1. Physical Characteristic

The Physical Characteristic was carried in all trial batches their physical characteristic is obtained appearance is clear & Homogenicity is Homogenous. shown in table no 6.

3.5.2.pH

The pH values of 1% aqueous solutions of the prepared nanogels of trial batches was obtained in between 6 to 7. Shown in table no 6.

3.5.3.Viscosity

The viscosity of the formulated batches was Obtained in between 181.7 to 181.9 Poiseiulle (PI).Maximum viscosity is 181.9 & minimum viscosity is 181.7. shown in table no 6.

3.5.4. Spreadability

Spreadability of trial batches formulation was obtained in between 0.62 to 1cm
Which is shown in table no 6.

3.5.5.Extrudability

The extrudability of the trial batches formulation was obtained in terms of weight in grams which is obtained in between 253 to 295 shown in table no 6.

3.5.6.% Drug Content

The % Drug Content of the trial batches formulation was obtained in between 92 to 95% which is shown in table no 6.

3.5.7. Measurement of particle size of formulation

Particle size of the trial batches formulation is obtained in between 300 to 600nm.

3.5.8.In vitro Release studies

In vitro drug release study of optimized batch A1 shown in figure no 7.

Table No.7.In vitro Release studies

SR NO	TIME INTERVAL	% DRUG RELEASE		
		A 1	A 2	A 3
1	0	0	0	0
2	20	21	25	22
3	40	29	33	31
4	60	40	44	43
5	80	53	59	55
6	100	59	65	62
7	120	63	70	66
8	140	79	86	82
9	160	85	95	90
10	180	88	97	92

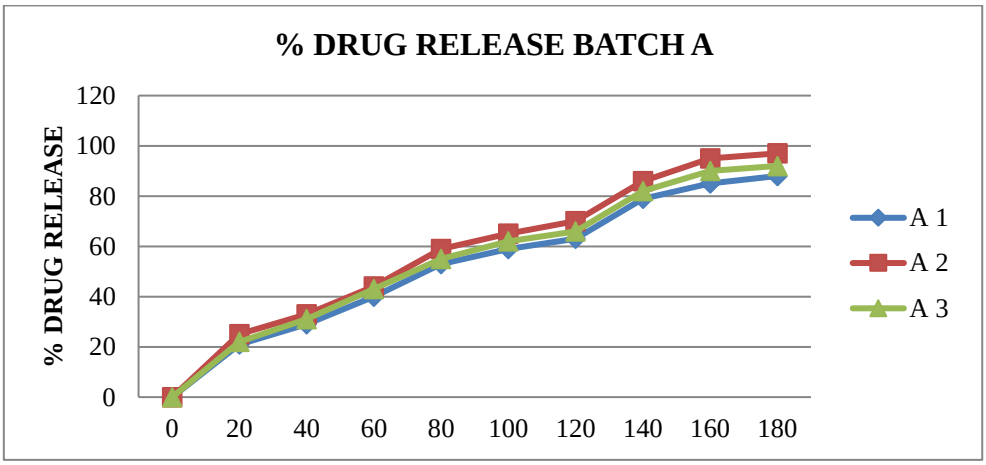

Fig 6: Drug Release Profile of Batch A

Table No.8. *In vitro* Release studies

SR NO	TIME INTERVAL	% DRUG RELEASE		
		B 1	B 2	B 3
1	0	0	0	0
2	20	22	22	23
3	40	27	30	33
4	60	41	42	45
5	80	50	53	56
6	100	55	60	66
7	120	62	65	71
8	140	75	79	80
9	160	83	84	87
10	180	87	89	91

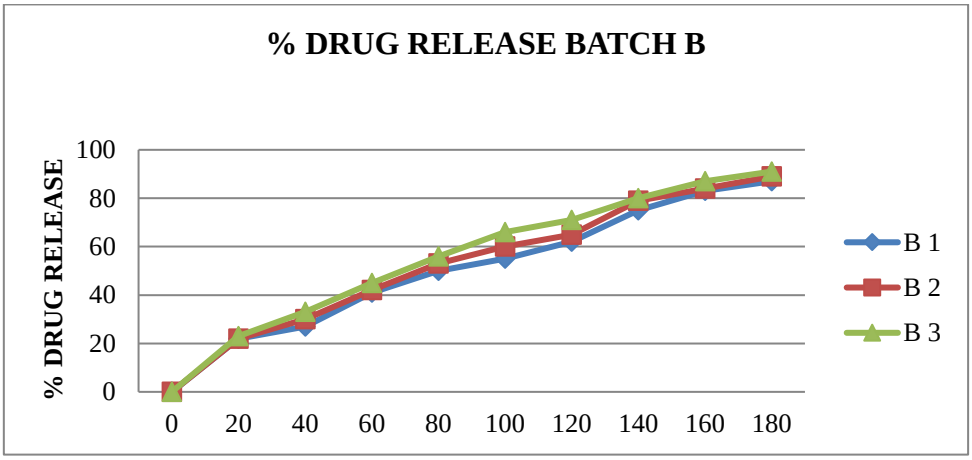

Fig 6: Drug Release Profile of Batch B

Table No.9.*In vitro* Release studies

TIME INTERVAL	% DRUG RELEASE		
	C 1	C 2	C 3
0	0	0	0
20	21	22	23
40	29	32	34
60	44	45	46
80	53	54	58
100	57	63	68
120	64	67	73
140	79	82	83
160	86	85	86
180	89	90	93

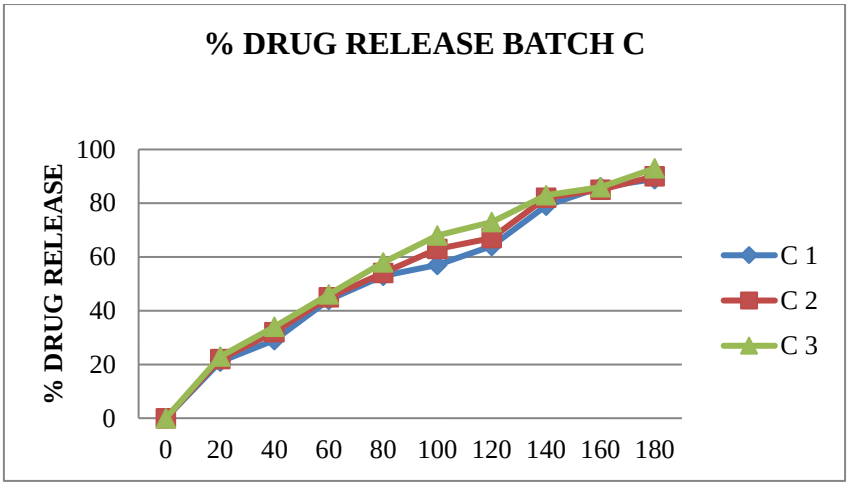

Fig 6: Drug Release Profile of Batch C

3.5.9.Skin Irritation

Skin irritation study of trial batches formulation is not irritant all the batches are not irritant to the

3.5.10.Stability Study

stability batches From the evaluation parameter result of trial batches we found Batch-A2 as the optimized batch and further experimental design is formulated. Figure . The evaluation parameter performed for the trial batches (B and C) are the same as done for the above prototype batch (A) and they are appearance, homo-geneity, particle size measurement, pH measurement, drug entrapment efficiency, drug content, in vitro drug release, skin irritation study, spreadibility, extrudability, rheological study,

stability batches From the evaluation parameter result of trial batches we found Batch-A2 as a optimized batch and further experimental design is formulated.

Fig 7: Benzocaine Nanogel Formulation

Table No 8: Trial Batches Evaluation Results

Nanogel	Physical Appearance	pH	Viscosity at 30rpm	Spreadability (g.cm/s)	Extrudability (g)	% Drug content
A1	Clear & homogenous	6.9	181.8	1	265	93.5
A2	**Clear & homogenous**	**6.2**	**181.8**	**0.83**	**295**	**97.8**

A3	Clear & homogenous	6	181.7	0.73	253	95.05
B1	Clear & homogenous	7.9	181.9	0.8	275	92.8
B2	Clear & homogenous	7.8	181.8	0.72	265	92.6
B3	Clear & homogenous	7.8	181.9	0.79	255	92.8
C1	Clear & homogenous	6.9	181.7	0.66	274	92.2
C2	Clear & homogenous	6.8	181.6	0.62	263	92.6
C3	Clear & homogenous	6.8	181.7	0.63	257	92.5

4. Summary & Conclusion

The Origin of research work starts from literature review. It is often difficult to start the work inparticular direction if bypassed literature review. By considering the same thing, prove literature review was carried out.The present work involves the formulation development, optimization and evaluation of Benzocaine nanoparticles loaded Nano gel. The benzocaine loaded Nanogel were prepared by Emulsion Solvent Diffusion Method and optimized .Various concentration of Eudragit-L-100 & Tween 80 is used to prepare nanoparticles. Total 10formulations were formulated and evaluated for different evaluation parameters like apperance, homogeneity, pH of Nanogel, spreadability determination, stability studies, Drug content, visco and particle size. The Benzocaine and Excipients like Eudragit -L-100, Tween 80, Carbapol 934, glycerol, propylene glycol were found to be compatible in FTIR study showed that prepared nanoparticles were spherical in shape with a smooth surface with spherical shape. Particle size of prepared nanoparticles was found to be in the range between 155nm and 335.5nm.In-vitro drug release of the optimized formulation shows 99.87% release at the end of 12 hours. Using Reverse micellar method usedto assess the Relationship between factors and response significantly. The final formula prepared with the predicted one based on expected values and the observed value pretty similar. It can therefore be inferred that prepared Benzocaine loaded with Nano gel was a suitable candidate for a topical drug delivery System.

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