



FORMULATION AND EVALUATION OF ANTI INFLAMMATORY GUGGULUOSOMAL GEL.

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ABSTRACT

Novel drug delivery System adopts various strategies to achieve controlled and targeted drug delivery. Guggulosomes are the vesicular drug delivery systems wherein the guggul lipids when triturated with the solution of the drug form drug entrapped vesicles. Guggulosomes can be utilized for therapeutic and cosmetic purpose for the delivery of the active. Guggul lipid is the standardized extract of the oleo-gum-resin of *Commiphora mukul*, family - *Burseraceae*. Scientific investigations of guggul lipid indicated it to possess anti-inflammatory, hypolipidemic, anti-obesity and anti-cancer; anti-wrinkle & anti-acne activities. Guggulosomes act synergistically when formulated for treatment of the above conditions. The aim of the present study is to formulate and evaluate guggulosomes of diclofenac sodium and piroxicam with an objective to reduce the dose required to elicit

therapeutic effect. Guggulosomes are prepared using sonication method and trituration method. In the present study guggulosome are prepared by trituration method using different drug lipid ratios. All the formulated guggulosomes were evaluated for morphology, SEM, Zeta potential, entrapment efficiency and in-vitro drug release. Evaluation data indicated diclofenac sodium guggulosome formulation F4 to be best with entrapment efficiency & % cumulative drug release of 92.5 ± 0.361 & 90.5 ± 5.2 respectively. F8 formulation of piroxicam guggulosome was selected as it has shown highest entrapment efficiency and % drug release of 95.54 ± 0.251 & 95 ± 5.4 respectively. Therefore F4 & F8 were selected for formulation as topical gels. The gels were formulated using carbapol 943 & HPMC E5 by dispersion method. All the gels were evaluated for visual appearance, pH, viscosity, spreadability & invitro drug diffusion studies. G1 (diclofenac guggulosomal gel)

demonstrated highest drug content & % drug release of 99.87 & 82±4.4 in 8 hours respectively. G5 formulation of topical piroxicam guggulosomal gel demonstrated highest drug content and % drug release of 99.77 & 86.52±2.6 in 8 hours respectively. The selected guggulosomal formulations G1 & G5 were compared with the marketed diclofenac sodium gel (Voltaren gel) & piroxicam gel (Felden gel). The results obtained show that the formulated gels have sustained drug release. However further animal studies are required to demonstrate the cumulative anti inflammatory action of the lipid.

KEYWORDS: Guggulosomes, phospholipids, guggul lipids, anti-inflammatory.

INTRODUCTION

Novel drug delivery systems are designed to delivery the drug at predetermined time over an extended period of time to achieve desired therapeutic efficacy and minimize side effects. Vesicular drug delivery systems can be defined as highly ordered assemblies consisting of one or more concentric bilayers formed as a results of self assembling of amphiphilic buliding blocks in presence of water. Guggulosomes are the vesicular drug delivery system wherin the guggul lipid when triturated with solution of the drug form drug entrapped vesicles. Guggul is an oleo-gum-resin obtained from plant *Commiphora wightii* or *Commiphora mukul* (Family-*Burseraceae*). Its active are two stereoisomers, *E*-guggulsterone and *Z*-guggulsterone. Guggul is used in Ayurvedic medicines for treatment of many ailments such as rheumatism, arthritis, hypolipidemia, obesity, inflammation, atherosclerosis, wrinkles, acne etc. Lipids are used in drug delivery for making liposome's, niosomes, nanoparticles, microemulsion, multiplemulsion and solid lipid nanoparticles. Therefore Guggul, due to its lipid content guggulsterones E&Z can also be used in making vesicular drug delivery systems. Guggulosomes are non-toxic and bio compatible.

Guggulosomes are prepared by sonication and trituration method. Milky dispersion is formed when guggul is triturated with water. This dispersion were viewed under microscope showed the presence of tiny globules, particles or vesicles. The trituration of the drug with guggul in presence of water results in the uptake of the drugs into the vesicles. This uptake of the drug is shown by both hydrophilic and lipophilic materials. This property of guggul is similar to the liposome forming behavior of phospholipids.

Diclofenac sodium is a non steroidal anti inflammatory drug. Diclofenac is used to relieve pain, swelling (inflammation) and joint stiffness caused by arthritis. Diclofenac sodium is

formulated in the form of tablets and gels. Piroxicam is a cyclooxygenase inhibiting NSAID used in treatment of rheumatoid arthritis, osteoarthritis, musculoskeletal disorders and post operative pain. Piroxicam is available in the form of tablets, capsules and gels. Piroxicam long half life enables it to administered once daily.

The aim of the present study is to formulate and evaluate anti inflammatory guggulosomal gels. Formulation with guggul lipid exerts synergistic activity and therefore the dose required to exert therapeutic activity will be reduced. The objective is two fold: One to reduce the drug dose & second to demonstrate synergistic activity.

MATERIALS AND METHOD

Materials

Guggul was procured from Green heaven India, Maharashtra. Diclofenac sodium & Piroxicam was procured from S.A. Dine-chem. Ltd India. Carbapol 934 and HPMC E5 were procured from BMR chemicals and other chemicals used were of reagent grade.

Method

Determination of λ_{\max} of Diclofenac & Piroxicam

Spectrophotometric analysis indicated λ_{\max} of Diclofenac sodium & piroxicamin phosphate buffer pH 6.8 as 276 & 354nm respectively. Standard graph yielded linear equation $y=0.0521\pm 0.0505$ & $y=0.062\pm 0.009$ respectively. The co-relation coefficient obtained were 0.9998 & 0.9991 respectively.

Method of preparation of guggulosomesof diclofenac and piroxicam.

Trituration method

Sufficient quantity of drugs diclofenac sodium and piroxicam are dissolved in little amount of water. Guggul lipid is dissolved in span 80 and ethanol. Drug solution is added to guggul lipid by trituration. Adjust the volume with distilled water. Continuous triturating results in fine uniform vesicles.

Table 1: Composition of guggulosomal formulations of diclofenac sodium: F1-F4.

	F1	F2	F3	F4
Diclofenac sodium	100mg	100mg	100mg	100mg
Guggul lipid	50mg	100mg	150mg	200mg
Ethanol	4ml	4ml	4ml	4ml
Span 80	5%	5%	5%	5%
Water	Upto 20ml	Upto 20ml	Upto 20ml	Upto 20ml

Table 2: Composition of guggulosomal formulations of piroxicam: F5-F8.

	F5	F6	F7	F8
Piroxicam	50mg	50mg	50mg	50mg
Guggul lipid	50mg	100mg	150mg	200mg
Ethanol	4ml	4ml	4ml	4ml
Span 80	5%	5%	5%	5%
Water	Upto 20ml	Upto 20ml	Upto 20ml	Upto 20ml

Evaluation of guggulosomes

Visual microscopy

A drop of guggulosomal suspension is placed on the glass slide and observed under optical microscope and photographs were taken with a digital camera.

Scanning electron microscopy

The morphology of guggulosomes were determined using SEM. 1 drop of guggulosomal suspension was taken on a clear glass tube and visualised under scanning electron microscope.

Zeta potential

Zeta potential was determined using zetasizer. 1 ml of guggulosomal suspension was taken and inserted into zeta cell using disposable syringe. Zeta potential is measured using light scattering method.

Vesicle size

In size mode of zeta sizer vesicle size was measured. 1 ml of guggulosomal suspension was taken and inserted into zeta cell and analysed using He-Ne laser at scattering angle of 175° at 25°C.

Drug-excipient compatability studies

Drug-excipient interaction studies were carried out by FTIR analysis. The IR spectrum of the pure drug was compared with IR spectrum of guggulosomal suspension of diclofenac sodium and piroxicam. 1 drop of guggulosoma lsuspension was taken and was mixed thoroughly with 100mg potassium bromide IR powder. IR spectrum was recorded from 4000 cm⁻¹ to 400cm⁻¹.

Entrapment efficiency

Guggulosomal suspension was taken in a test tube and centrifuged at 15000rpm for 90mins. Supernant liquid was pipetted out and transfered to 10ml volumetric flask and diluted with

phosphate buffer pH 6.8. Concentration of the entrapped or free drug present in supernatant was determined by measuring absorbance at 276nm for guggulosome of diclofenac sodium and 354nm for guggulosome of piroxicam using double beam UV-spectrophotometer.

The percentage of encapsulation efficiency was determined by the following equation:

$$EE (\%) = \frac{W_{tot} - W_{free}}{W_{tot}} \times 100$$

Here, W_{tot} = amount of total drug, W_{free} = amount of the free drug.

Invitro drug release studies

The in vitro drug diffusion study of guggulosomal suspension were conducted using franz diffusion cell. Gelatin membrane of pore size 2.4nm was used as a diffusion membrane. 1 ml of guggulosome suspension was placed on donor compartment of the diffusion cell. The phosphate buffer 6.8 was kept in receiver compartment and stirred continuously at 500 rpm. From receptor compartment 1ml solution was withdrawn at 0,1,2,3,4,5,6,7,8 hours respectively and replaced by buffer solution so that volume of receptor solution kept constant during drug release. The aliquots were transferred to 10ml volumetric flask and made upto 10ml using phosphate buffer pH 6.8. The absorbance of sample was measured at the λ_{max} of the drugs. The in-vitro drug release was carried out in triplicate and results expressed as the mean \pm SD., and further the cumulative drug release was calculated and a plot of time versus %drug release was constructed.

Method of preparation of topical guggulosomal gels

Selected guggulosomes of diclofenac & piroxicam were used for preparation of guggulosomal gel. Equivalent volume of guggulosomal drug suspension was incorporated to prepare 1% of diclofenac gel & 0.5% piroxicam gel. The topical gels were prepared using HPMC E5 & carbapol934 in different concentrations. Gels were prepared by adding polymers to the distilled water. Then, propylene glycol was added as a humectant and the mixture was neutralized by drop wise addition of triethanolamine. Mixing was continued until a transparent gel appeared. Then allowed the mixture to stand overnight to get a uniform dispersion. After uniform dispersion guggulosomal suspension is added to the gel and sonicated.

Table 3: Composition of diclofenac guggulosomal gels: G1-G4.

	G1	G2	G3	G4
Diclofenac sodium guggulosomal suspension	4ml	4ml	4ml	4ml
Carbapol 934	1%	1.5%	---	---
Hpmc E5	---	---	8%	9%
Propylene glycol	2%	2%	2%	2%
Triethanolamine	0.5%	0.5%	0.5%	0.5%
Water(q.s)	20ml	20ml	20ml	20ml

Table 4: Composition of piroxicam guggulosomal gel: G5-G8.

	G5	G6	G7	G8
Piroxicam guggulosomal suspension	4ml	4ml	4ml	4ml
Carbapol 934	1%	1.5%	---	---
Hpmc E5	---	---	8%	9%
Propylene glycol	2%	2%	2%	2%
Triethanolamine	0.5%	0.5%	0.5%	0.5%
Water(q.s)	20ml	20ml	20ml	20ml

Evaluation of guggulosomal gel

Visual examination

Clarity, colour and homogeneity of the gel was examined under light against black and white back ground.

pH

1g of gel was transferred in 100ml of volumetric flask, and dissolved in small volume of phosphate buffer pH 6.8 and made upto 100ml using phosphate buffer pH 6.8. The pH of the gel was determined using systronic pH meter and the reading was noted. The results were obtained in triplicate. Mean and standard deviation were calculated.

Drug Content

1 gram of the gel was taken and dissolved in 10ml buffer (pH 6.8). The solution was sonicated for 15 minutes. The resultant solution was filtered and absorbance was measured at λ_{\max} of diclofenac and piroxicam. The results were obtained in triplicate. Mean and standard deviation were calculated.

Determination of spreadability

One gram of gel is placed between two plates of 20×20cm. After one minute the spreading diameter was measured. The spreadability was calculated by using the following formula.

$$S = mt/l$$

Where S = spreadability, m = weight of upper slide, l = length of the glass slide, t = time.

The results were obtained in triplicate. Mean and standard deviation were calculated.

Viscosity

A Brookfield viscometer was used to measure the viscosities of all the formulations of gel prepared. A spindle (LV1) was rotated at 50rpm. The results were obtained in triplicate. Mean and standard deviation were calculated.

In Vitro Drug diffusion Studies

The in vitro drug diffusion study of guggulosomal gel were conducted using franz diffusion cell. Gelatin membrane of pore size 2.4nm was used as a diffusion membrane. 1 ml of gel was placed on donor compartment of the diffusion cell. The phosphate buffer 6.8 was kept in receiver compartment and stirred continuously at 500 rpm. From receptor compartment 1ml solution was withdrawn at 0,1,2,3,4,5,6,7,8 hours respectively and replaced by buffer solution so that volume of receptor solution kept constant during drug release. The aliquots were transferred to 10ml volumetric flask and made upto 10ml using phosphate buffer pH 6.8. The absorbance of sample was measured at the λ_{max} of the drugs. The study was carried out in triplicate and results expressed as the mean \pm SD., and further the cumulative drug release was calculated and a plot of time versus %drug release was constructed.

RESULTS AND DISCUSSION

Evaluation of guggulosomes of diclofenac sodium & piroxicam

Visual microscopy

Visual microscopy indicated vesicle formulations in all the formulations.

Scanning electron microscopy

The SEM image is shown in the fig 1 and 2. The microscopic view of the diclofenac sodium guggulosomes(F4) and piroxicam guggulosomes(F8) indicated the presence of sphere shaped vesicles.

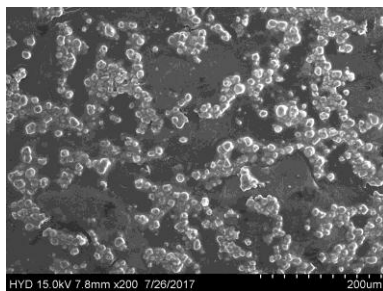


FIG 1: SEM Image of diclofenac guggulosomes.

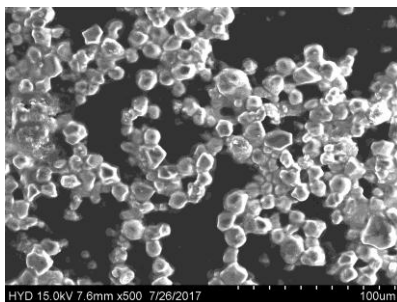


FIG 2: SEM Image of piroxicam guggulosomes.

Zeta potential

The zeta potential value diclofenac sodium formulation (F4) and piroxicam (F8) was found to be -26.mV &- 31.2mV respectively as indicated in table 3 & 4. The values indicate both guggulosomal formulation to have good stability. The vesicles had sufficient negative charge present on their surface to prevent the collision and aggregation.

Table 3: Zeta potential of diclofenac sodium guggulosomes.

Calculation Results		
Peak No.	Zeta Potential	Electrophoretic Mobility
1	-26.2 mV	-0.000203 cm ² /Vs
2	-- mV	-- cm ² /Vs
3	-- mV	-- cm ² /Vs
Zeta Potential (Mean)		: -26.2 mV
Electrophoretic Mobility mean		: -0.000203 cm ² /Vs

Table 4: Zeta potential of piroxicam guggulosomes.

Calculation Results		
Peak No.	Zeta Potential	Electrophoretic Mobility
1	-31.2 mV	-0.000242 cm ² /Vs
2	-- mV	-- cm ² /Vs
3	-- mV	-- cm ² /Vs
Zeta Potential (Mean)		: -31.2 mV
Electrophoretic Mobility mean		: -0.000242 cm ² /Vs

Vesicle size

Fig 3 & 4 shows the vesicle sizes of selected diclofenac guggulosomes (F4) and piroxicam guggulosome (F8). The average size were found to be 554.2nm and 282.2nm respectively

with poly dispersity index 0.162 & 0.849 respectively. The results indicated that the diclofenac sodium guggulosomes and piroxicam guggulosomes are in monodispersive range and vesicle size are in narrow range.

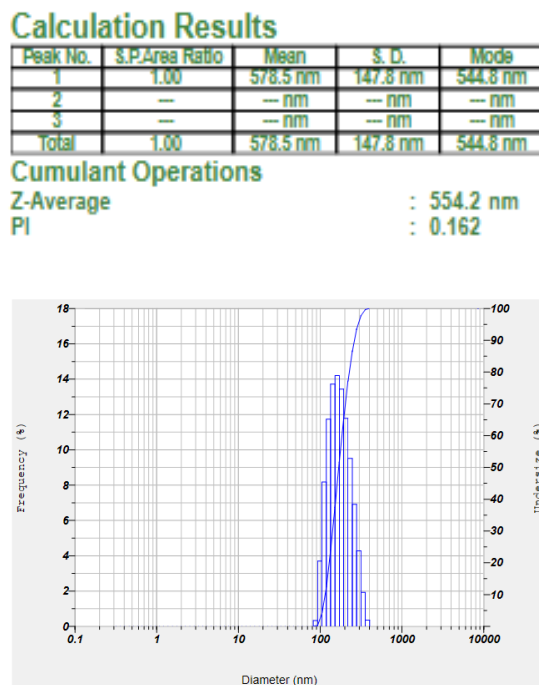


Fig 3: Vesicle size of diclofenac sodium guggulosomes.

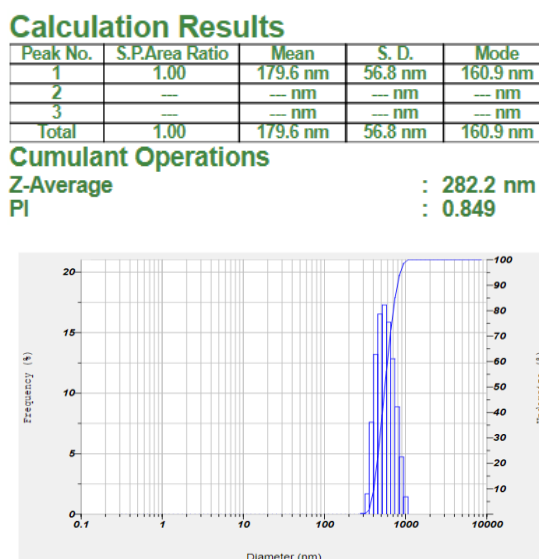
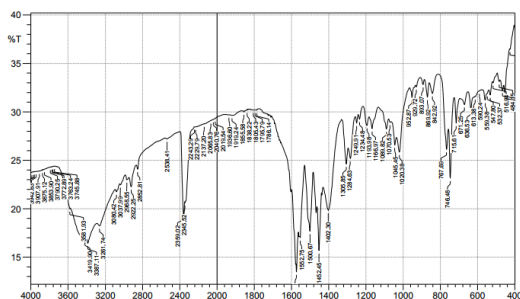
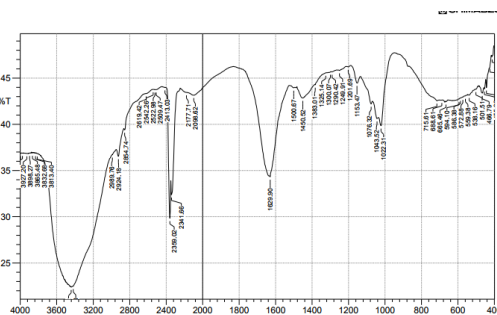
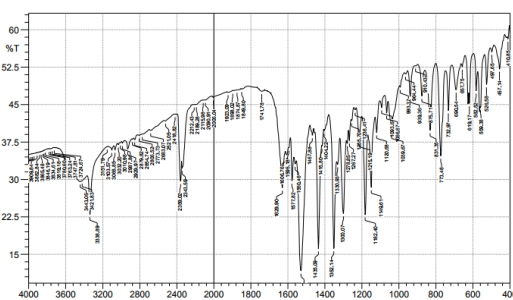
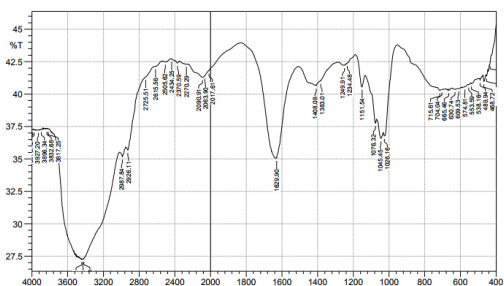


Fig 4: Vesicle size of piroxicam guggulosomes.

Drug-polymer Interaction Studies

Fig 5-fig8 are the IR spectrum of pure drugs (diclofenac & piroxicam) and guggulosomal suspensions. The spectrum indicated neither appearance nor disappearance of peaks which confirmed the absence of any chemical interaction between the drug and lipid/ excipients.

**FIG 5: FTIR spectrum of diclofenac sodium drug.****FIG 6: FTIR spectrum of diclofenac sodium guggulosomal suspension.****FIG 7: FTIR spectrum of piroxicam drug.****FIG 8: FTIR spectrum of piroxicam guggulosomal suspension.**

Entrapment efficiency

The entrapment efficiency of all formulations are tabulated in table 5 & 6. The guggulosomes containing high amount of guggul lipid showed high entrapment efficiency. F4(diclofenac guggulosomes) & F8(piroxicam guggulosomes) exhibit the highest entrapment efficiency of 92.50 & 95.54 respectively. This can be explain as the drug and lipid ratio increases no of vesicles formed also increases which results in more entrapment of the drug.

Table 5: %EE of diclofenac sodium guggulosomes.

Formulation	%EE \pm SD*
F1	23.86 \pm 0.282
F2	50.73 \pm 0.560
F3	73.00 \pm 0.212
F4	92.50 \pm 0.316

*Results are the mean of three readings (n=3).

Table 6: %EE of piroxicamguggulosomes.

Formulation	%EE \pm SD*
F5	35.11 \pm 0.84
F6	68.98 \pm 0.56
F7	79.00 \pm 0.162
F8	95.54 \pm 0.215

*Results are the mean of three readings (n=3).

Invito drug release

The in-vitro drug release profile of both formulations were recorded in table 7&8. The experimental data indicated that formulation F4 & F8 showed higher cummulative drug release of 90.51 \pm 5.2 & 95 \pm 5.4 in 8 hours respectively. The experimental studies showed that the rate of drug release depends on the drug concentrations in the formulations. In F4 & F8 the entrapped % drug is greater which explains high % drug release.

Table 7: Cumulative %drug release of diclofenac sodium guggulosomes.

Time (hr)	F1 \pm SD*	F2 \pm SD*	F3 \pm SD*	F4 \pm SD*
0	0	0	0	0
1	5.04 \pm 4.5	6.00 \pm 5.2	8.32 \pm 5.3	13.80 \pm 5.6
2	8.20 \pm 4.3	9.32 \pm 5.4	11.20 \pm 4.4	32.16 \pm 5.4
3	14.30 \pm 5.8	15.80 \pm 5.1	17.40 \pm 4.8	46.40 \pm 5.3
4	19.21 \pm 4.8	21.50 \pm 4.8	24.30 \pm 5.3	56.80 \pm 5.3
5	24.03 \pm 4.6	33.30 \pm 4.7	36.64 \pm 5.1	68.00 \pm 4.7
6	32.16 \pm 4.4	44.60 \pm 4.5	45.50 \pm 4.7	76.51 \pm 4.6
7	32.16 \pm 4.4	53.56 \pm 5.5	56.60 \pm 4.3	80.30 \pm 4.5
8	43.00 \pm 4.6	62.90 \pm 5.4	76.00 \pm 4.6	90.51 \pm 5.2

*Results are the mean of three readings (n=3).

Table 8: Cumulative % drug release of piroxicam guggulosomes.

Time	F5 ± SD*	F6 ± SD*	F7 ± SD*	F8 ± SD*
0	0	0	0	0
1	1.80±1.2	2.60±2.0	13.81±4.4	13.60±5.2
2	5.04±5.3	11.21±5.7	32.16±4.8	23.72±5.4
3	10.64±4.4	17.40±4.8	46.40±4.6	33.81±5.1
4	16.44±4.5	24.30±3.4	56.83±4.3	45.10±4.8
5	24.00±4.6	34.64±4.2	68.00±3.7	54.86±4.7
6	32.08±4.3	45.50±4.5	76.59±4.8	74.12±4.5
7	43.92±4.4	56.61±4.6	80.31±5.4	80.25±5.5
8	55.32±2.6	76.00±4.3	86.42±4.5	95.00±5.4

*Results are the mean of three readings (n=3).

Based on the evaluation data F4 (diclofenac guggulosomes) & F8 (piroxicam guggulosomes) have been selected for formulation as guggulosomal gels.

Evaluation of topical guggulosomal Gel

Visual examination

All formulations were opaque, yellow, smooth to touch and free from grittiness.

pH

pH of all formulations were found to be in the range of 6.7 which is close to skin pH and ideal for skin application.

Drug Content

Drug content was tabulated in Table 11 & 12. Results revealed that the drug content of the selected formulation G1 and G5 was found to be 99.87% and 99.77% respectively.

This ensures intended delivery of drug to the site after administration of the gel formulation.

Table 11: Drug content of diclofenac sodium guggulosomal topical gel.

S.no	Formulation	%Drug content
1	G1	99.87
2	G2	98.54
3	G3	95.32
4	G4	95.00

Table 12: Drug content of piroxicam guggulosomal topical gel.

S.no	Formulation	%Drug content
1	G5	99.77
2	G6	98.63
3	G7	96.23
4	G8	95.21

Spreadability

The topical guggulosomal gels G1 to G8 had optimum spreadability. There was no problem in the application of the gel. The gels when applied spread easily on the skin.

Viscosity

Viscosity studies demonstrated pseudoplastic behaviour of the gels which is ideal for application.

Invitro diffusion studies

The results of in vitro drug release of the guggulosomal gels are shown in table 17-18. Results indicated that G1(diclofenac gel) & G5(piroxicam gel) show highest % drug release of 82.00 & 86.52 in 8 hours respectively. This can be explained as G1 & G5 shows highest drug content and were formulated using 1% carbapol 934. As the concentration of carbapol increases viscosity increases and rate of drug diffusion decreases.

Table 17: Drug release profile of diclofenac sodium gels(G1-G4).

Time (hr)	G1	G2	G3	G4
0	0	0	0	0
1	10.8	9.00	5.31	3.21
2	23.54	18.21	11.00	9.71
3	35.68	26.33	20.31	18.32
4	49.11	32.11	29.00	28.11
5	54.00	45.79	35.66	35.43
6	62.82	53.81	41.83	43.44
7	73.54	64.00	52.73	50.00
8	82.00	79.21	65.00	59.31

Table 18: Drug release profile of piroxicam gels(G5-G8).

Time (hr)	G5	G6	G7	G8
0	0	0	0	0
1	16.11	9.80	5.04	1.80
2	20.20	18.40	8.20	5.04
3	35.45	26.11	15.84	10.64
4	42.96	36.60	21.56	24.00
5	50.10	44.80	33.32	32.08
6	57.00	60.84	44.61	33.92
7	67.10	70.89	53.65	45.32
8	86.52	79.52	62.90	55.44

Comparative study of the optimized formulation with marketed formulation.

For comparative study the drug release profile of G1(diclofenac guggulosomal gel) and G5(piroxicam guggulosomal gel) are compared with the marketed formulated gels of diclofenac sodium (**Voltaren gel**) and piroxicam (**Felden gel**). The results obtained

indicated that the topical gels prepared show good sustain release activity compare to the marketed formulation. Further animal studies are required to show synergistic activity.

Table 19: Comparative study of invitro drug release of the optimized formulation and marketed formulation.

Time (hr)	G1	Markated diclofenac gel(Voltaren gel)	G5	Markated piroxicam gel(Felden gel)
0	0	0	0	0
1/2	-	56.00	-	54.21
1	10.8	76.48	16.11	73.53
1 1/2	-	89.52	-	82.48
2	23.54	99.66	20.20	98.32
3	35.68	-	35.45	-
4	49.11	-	42.96	-
5	54.00	-	50.10	-
6	62.82	-	57.00	-
7	73.54	-	67.10	-
8	82.00	-	86.52	-

CONCLUSION

Diclofenac & piroxicam guggulosomal gels were formulated. The optimum drug lipid concentration was found to be 1:4 as these formulation exhibited high entrapment efficiency % drug release. These guggulosomes (F4 & F8) were further formulated into topical gels. The gels were evaluated & % drug release was compared with marketed formulation voltaren gel & felden gel. These studies demonstrated that guggulosomal gels exhibited sustain release. Further animal studies are required to demonstrate synergistic activity of guggulosomal formulation.

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