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FORMULATION AND DEVELOPMENT OF QUERCETIN AND MONOAMMONIUM GLYCYRRHIZINATE LOADED GEL FOR THE TREATMENT OF MOUTH ULCER DISEASE

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Keywords:

Mouth ulcers RAS, Quercetin, Monoammonium Glycyrrhizinate

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ABSTRACT: Diagnosis of oral ulcerative lesions might be quite challenging. Oral ulcerative lesions were categorized into three major groups as acute, chronic, and recurrent ulcers. *Helicobacter pylori* (*H. pylori*) have been found in the oral cavity and stomach, and its infection is one of the most frequent worldwide. There is a close relation between *H. pylori* infection in the oral cavity and the stomach. *H. pylori* etiologic agent in recurrent apthous stomatitis, Canker sores. Quercetin inhibits the *H. Pylori*. Monoammonium glycyrrhizinate (MAG) was recognized as a compound possessing antimicrobial properties; MAG tested many researchers using the agar diffusion method which, show significant antibacterial activities against gram-positive (*Bacillus subtilis*, Stap *Hylococcus aureus*) as well as gram-negative bacteria (*Escherichia coli*, *Pseudomonas aeruginosa*). The objective of the present investigation was to formulate and evaluate gel for mouth ulcer treatment of Quercetin and MAG. The concentration of carbopol p940 and propylene glycol were optimized using a central composite design for two factors. Formulations were evaluated for various parameters such as pH, viscosity, spreadability, drug content, cumulative drug diffusion, Texture analyzer, *ex-vivo* permeation, and mucoadhesion. The developed formulation was stable, safe, and effective for the treatment of mouth ulcer.

INTRODUCTION: Ulcer means the break in the continuity of the epithelium brought about by molecular necrosis. Ulcers are most commonly occur in the oral region, for which the patient seeks help from their physician/dental surgeon. The presenting symptoms are usually redness, burning sensation and/or pain **Fig. 1**. They can present in any part of the oral cavity, but it becomes painful if it occurs in the movable area [1]. Mouth ulcers are very common and are usually occur due to trauma, such as from ill-fitting dentures, fractured teeth, or fillings **Fig. 2**.

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However, patients with an ulcer of over 3 week's duration should be referred for biopsy or other investigations to exclude malignancy or other serious conditions such as chronic infections. Ulcers related to trauma usually resolve within in a week after removal of the cause to maintain good oral hygiene [2]. MAG possesses a wide range of pharmacological and biological activities. It possesses anti-inflammatory activity, anti-ulcer, anti-bacterial, anti-allergic, antidote, antioxidant, antiviral, anti-tumour, anticonvulsant activity.

Drugs show anti-ulcer, anti-inflammatory, anti-bacterial, anti-viral, which play a major role in curing mouth ulcers, but the major reason for a section of this drug is its sweet test which is mainly not seen in other drugs, so this property increases patient compliance [3-7]. Quercetin chelates ions of transition metals such as iron which can initiate the formation of oxygen free radicals and inhibits

xanthine oxidase activity and nitric oxide-induced radical damage, all of which have been implicated in the etiopathogenesis of recurrent aphthous stomatitis. In addition, quercetin also inhibits the enzymes cyclooxygenase and lipooxygenase which catalyzes the conversion of arachidonic acid to its metabolites, suggesting it to be a potent anti-inflammatory agent Relative Efficacy of Quercetin [8-12].

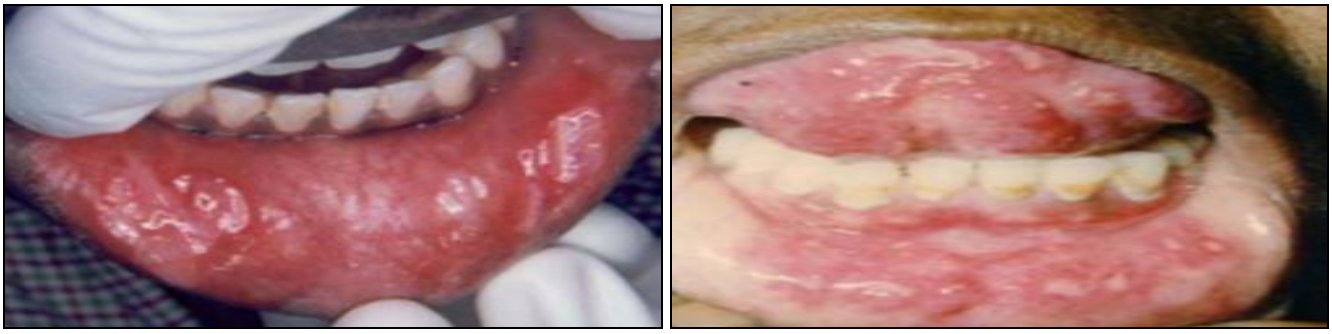


FIG. 1: APTHOUS MAJOR ULCER IN LOWER LABIALMUCOSA

FIG. 2: TRAUMA ULCER DURING TOOTH BRUSHING, FLOSSING

Topical Drug Delivery: Topical drug delivery systems are localized drug delivery systems for local delivery of therapeutic agents *via* skin to treat the cutaneous disorder. These systems are generally used for local skin infections. The formulations are available in different forms, like from solid through semisolid to liquid.

If the drug substance in the solution has a favorable lipid/water partition coefficient and if it is a non-electrolyte, then drug absorption is enhanced *via* the skin. Dermatological products have various formulations and range in consistency though the most popular derma products are semisolid dosage forms [13-14].

Advantages of Topical Drug Delivery Systems:

1. Avoidance of primary pass metabolism.
2. Convenient to use and easy to apply.
3. Easily to terminate the medications.
4. Drug delivered selectively to a specific site.
5. The gastro-intestinal incompatibility will be avoided.
6. Provides drug utilization with short biological half-life and narrow therapeutic window.
7. It provides effectiveness in low doses and by continuous drug input.
8. Avoids fluctuation in drug levels and risks.
9. A large area of application compared to other routes.
10. Drug delivery at a specific site

Disadvantages of Topical Drug Delivery Systems:

1. Possibility of local skin irritation at the site of application.
2. Contact dermatitis due to some drugs may occur.
3. Some drugs with poor permeability are difficult to penetrate via the skin.
4. Drugs with larger particle sizes are difficult to penetrate.
5. Possibility of allergenic reactions.

6. Drugs with a very small plasma concentration can be used for action

Types of Ulcer:

1. Acute Ulcer:

- ✓ Traumatic Ulcers
- ✓ Necrotizing Sialometaplasia
- ✓ Primary Herpetic Gingivostomatitis
- ✓ Varicella-Zoster Virus Infection
- ✓ Erythema multiforme
- ✓ Recurrent aphthous stomatitis [RAS]
- ✓ Behçet Disease [BD (Behçet Syndrome)]

2. Chronic Ulcer:

- ➢ Sustained traumatic ulcers (Decubitus ulcer)
- ➢ Squamous cell carcinoma
- ➢ Traumatic ulcerative granuloma (EosinopHilic ulcer of the tongue)

3. Pemphigus and Pemphigoid:

- Mucormycosis
- Tuberculous ulcers
- SypHilitic ulcers

MATERIALS AND METHODS:

Materials:

Drugs:

- ➢ Quercetin was obtained from Research Lab Fine Chem. Industries, Mumbai.
- ➢ Mono-ammonium Glycyrrhizinate was purchased from SV Agro Mumbai.

Chemicals: Carbopol 934, Propylene glycol, Sodium benzoate

Solvents: Ethanol, Water.

Method:

Preformulation Studies: [13, 15-17]

The aim of Preformulation studies is as follow:

- ✓ To check physiochemical characterization of a new drug.
- ✓ To establish compatibility with different excipients.

Description: The sample was evaluated visually for appearance, color, and odor.

UV-visible Spectroscopy:

Calibration Curve of Curcumin:

Preparation Stock Solution of Quercetin: Ethanol AR: 10 mg pure Quercetin was dissolved in 100 ml ethanol to get a 100 ug/ml stock solution. Prepare concentration of 2 µg/ml, 4 µg/ml, 6 µg/ml, 8 µg/ml and 10 µg/ml respectively. Then measured absorbance of prepared dilutions at the respective wavelength.

Preparation Stock Solution of Quercetin: In pH 6.8 Phosphate Buffer 10 mg pure Quercetin was dissolved in 10 ml ethanol, then volume makeup upto 100 ml with pH 6.8 Phosphate Buffer, to get a 100 ug/ml stock solution. Prepare concentration of 2 µg/ml, 4 µg/ml, 6 µg/ml, 8 µg/ml and 10 µg/ml respectively. Then measured absorbance of prepared dilutions at the respective wavelength.

Preparation Stock Solution of Monoammonium Glycyrrhizinate:

Preparation Stock Solution of Monoammonium Glycyrrhizinate: Ethanol AR 10 mg pure MAG was dissolved in 100 ml ethanol to get a 100 ug/ml stock solution. Prepared dilutions of 5 µg/ml, 10 µg/ml, 15 µg/ml, 20 µg/ml, 25 µg/ml, 30 µg/ml, 35 µg/ml and 40 µg/ml respectively. Then measured absorbance of prepared dilutions at the respective wavelength.

Preparation Stock Solution of MAG: In pH 6.8 Phosphate buffer, 10 mg pure drug of MAG was dissolved in 10 ml ethanol, then volume makeup upto 100 ml with pH 6.8 phosphate buffer, to get a 100 ug/ml stock solution. Prepare dilutions of 5 µg/ml, 10 µg/ml, 15 µg/ml, 20 µg/ml, 25 µg/ml, 30 µg/ml 35 µg/ml and 40 µg/ml respectively. Then measured absorbance of prepared dilutions at the respective wavelength.

Formulation Design:

Formulation of Gel by Different Concentrations:

Preparation of optimization of Formulation: [18] Prepare Gel with different concentrations of Gelling agent and penetration enhancer by using design expert. Carbopol in the range of 0.5-2% and propylene glycol in the range 3-7% **Table 1.**

TABLE 1: OPTIMIZING DESIGN VALUES OF CARBOPOL P940 AND PROPYLENE GLYCOL

Factor	Carbopol 940			Propylene Glycol		
Coded level	-1	0	+1	-1	0	+1
Actual level	0.5%	1.25%	2%	3%	5%	7%

Procedure for Formulation of Gel: [16]

- Gel formulations were prepared using carbopol P940 as gelling agents and Propylene Glycol as penetration enhancer.
- The carbopol P940 was mixed with Propylene Glycol in a beaker heated at 70 ºC and
- Quercetin and MAG in a suitable solvent (ethanol) were added to the is dispersion.
- The preservative sodium benzoate was dissolved in water using heat the solution was left to cool and then warmed to about 70 ºC with vigorously stirring using an electric stirrer.
- Resulting solution added to the above solution with stirring until a gel was formed **Table 2**.

TABLE 2: FORMULATION TABLE OF GEL WITH DIFFERENT CONCENTRATION OF CARBOPOL P340 ANDPG

Ingredients	Different Batches of Formulation (Concentration in Percentage)								
	F 1	F 2	F 3	F 4	F 5	F 6	F 7	F 8	F 9
Quercetin	1%	1%	1%	1%	1%	1%	1%	1%	1%
Monoammonium Glycyrrhizinate	1%	1%	1%	1%	1%	1%	1%	1%	1%
Carbopol 940	0.5	1.25	2	1.25	0.189	2.310	2	1.25	0.5
Propylene glycol	7	5	3	2.17	5	5	7	7.8	3
Distill Water	q.s 100 ml	q.s 100 ml	q.s 100 ml	q.s 100 ml	q.s 100 ml	q.s 100 ml	q.s100 ml	q.s 100 ml	q.s100 ml

Evaluation of Gel: [19-22]

1. pH
2. Spreadability test.
3. Drug content test.
4. *In-vitro* drug diffusion study studies.

Finalization of Batch: Finalization of batch depends on various evaluations of all nine (F1-F9) batches.

From evaluation parameters which batch fulfill all evaluation parameters, this batch selected as optimized batch.

Evaluation of Optimized Gel: [23-29s]

1. Viscosity **Table 13**.
2. Texture analyzer **Table 12, Fig. 6.**
3. *Ex-vivo* drug permeation **Table 14**, **Graph. 3**.
4. Mucoadhesive strength determination **Table 15.**
5. Antimicrobial study **Table 16, Fig. 7.**
6. Stability testing **Table 17, 18**.
a) pH
b) Spreadability
c) Percentage drug content

RESULTS:

Physical Properties of Drug:

TABLE 3: APPEARANCE OF QUERCETIN AND MONOAMMONIUM GLYCYRRHIZINATE

Physiochemical Properties	Quercetin		MAG	
	Reported	Observed	Reported	Observed
Appearance	Light yellowish orange color powder with characteristic odor.	Bright yellow-orange powder with characteristic odor	White powder with characteristic odor.	White powder with a pleasant odour.

UV-visible Spectroscopy:

Summary of Validation Parameter:

TABLE 4: SUMMARY OF VALIDATION PARAMETER OF QUERCETIN AND MAG IN ETHANOL (AR)

S. no.	Parameter	Result of Curcumin	Result of MAG
1	Absorption maxima (ƛmax)	377nm	248 nm
2	Linearity Range (µg/ml)	2-10	10-50

3	Correlation Coefficient (R^2)	0.996	0.9969
4	Standard regression equation	y = 0.0269	y = 0.0118x
5	Intercept	-	-
6	Slope	0.9976	0.0118

TABLE 5: SUMMARY OF VALIDATION PARAMETER OF QUERCETIN AND MAG IN pH 6.8 PHOSPHATE BUFFER

S. no.	Parameter	Result of Curcumin	Result of MAG
1	Absorption maxima (λ_{max})	372nm	248 nm
2	Linearity Range (µg/ml)	2-10	10-50
3	Correlation Coefficient (R^2)	0.9979	0.9946
4	Standard regression equation	y = 0.0577x + 0.0018	y = 0.0129x
5	Intercept	0.0018	-
6	Slope	0.0577	0.0129

TABLE 6: pH OF DIFFERENT FORMULATION OF GEL

Formulation No.	1	2	3	Mean PH	S. D
F1	7.09	7.24	7.3	7.21	7.21±0.12
F2	6.9	6.6	7.2	6.9	6.9±0.300
F3	6.56	6.65	6.68	6.63	6.63±0.0700
F4	6.8	7.05	7.06	6.97	6.97±0.17
F5	7.35	7.09	7.25	7.23	7.23±0.14
F6	6.99	7.15	7.4	7.18	7.18±0.220
F7	6.74	6.89	6.77	6.8	6.8±0.0899
F8	6.95	6.5	6.74	6.73	6.73±0.23
F9	7.01	6.73	6.84	6.86	6.86±0.15

TABLE 7: SPREADABILITY OF DIFFERENT FORMULATION OF GEL

Formulation No.	1	2	3	Mean Diameter	S. D
F1	3.9	3.85	4.04	3.93	3.93±0.11
F2	3.27	3.25	3.53	3.35	3.35±0.18
F3	2.42	2.8	3	2.74	2.74±0.32
F4	5.98	5.9	6.06	5.98	5.98±0.080
F5	5.56	5.47	5.65	5.56	5.56±0.090
F6	2.86	2.8	2.92	2.86	2.86±0.060
F7	6.3	6.5	6.1	6.3	6.3±0.2
F8	4.9	5.1	4.7	4.9	4.9±0.2
F9	7.5	7.7	7.3	7.5	7.5±0.2

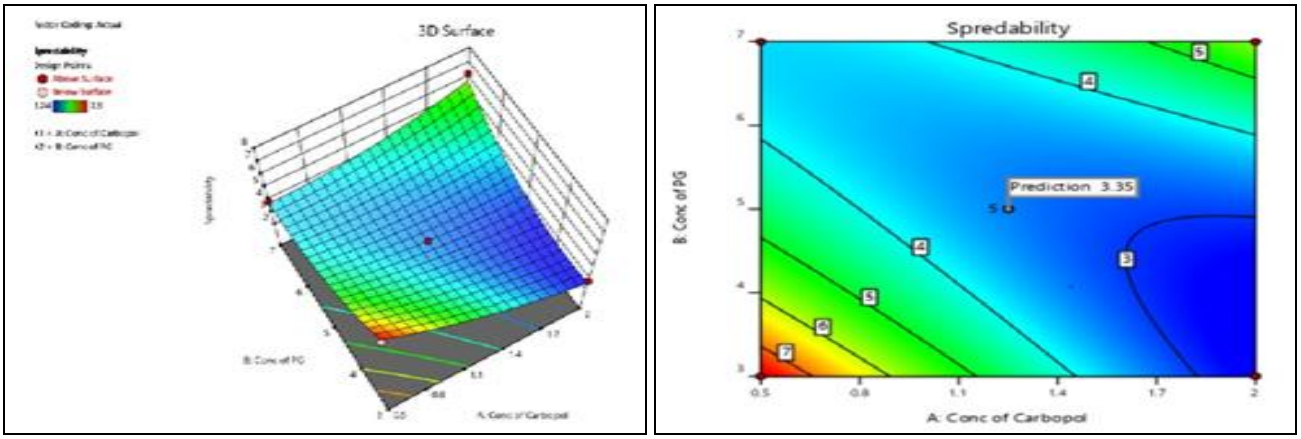


FIG. 3D AND 2D: PLOT FOR EFFECT OF CONCENTRATION OF CARBOPOL AND CONC. OF PG ON SPREADABILITY

TABLE 8: PERCENTAGE DRUG CONTENT OF QUERCETIN FOR DIFFERENT FORMULATION OF GEL

Formulation No.	1	2	3	Mean % Drug Content	S. D
F1	99.1	97.62	96.5	97.74	97.74±1.359
F2	99.04	97	99.28	98.44	98.44±1.440
F3	95.6	97.2	96.28	96.36	96.36±0.839

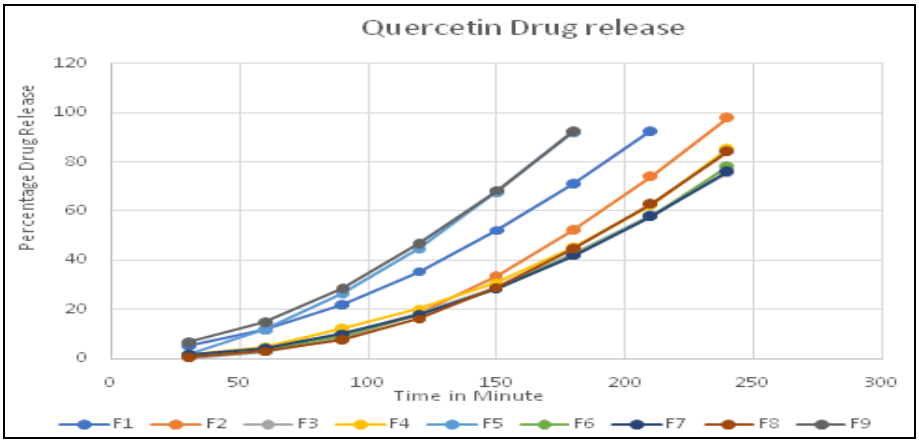
F4	99.65	99.96	99.35	99.653	99.653±0.306
F5	92.7	94.85	93.2	93.583	93.583±1.266
F6	96.5	97.05	97.6	97.05	97.05±0.549
F7	88.96	92.6	88.8	90.12	90.12±2.47
F8	91.56	92.3	89.62	91.16	91.16±1.540
F9	95.5	93.13	92.12	93.583	93.583±1.916

TABLE 9: PERCENTAGE DRUG CONTENT OF MAG FOR DIFFERENT FORMULATION OF GEL

Formulation No.	1	2	3	Mean % Drug Content	S. D
F1	96.5	91.26	95.96	94.57	94.57±3.30
F2	97.87	97	95.8	96.89	96.89±1.09
F3	88.5	93.12	95.1	92.24	92.24±3.74
F4	91.9	94.25	92.92	93.023	93.023±1.22
F5	92.7	93.18	93.2	93.026	93.026±0.32
F6	90.57	88.59	90.6	89.92	89.92±1.33
F7	96.5	94.23	97.65	96.12	96.12±1.89
F8	91.56	88.58	89.62	89.92	89.92±1.64
F9	88.9	88.5	87.71	88.37	88.37±0.66

TABLE 10: % DRUG RELEASE OF QUERCETIN FROM DIFFERENT GEL FORMULATION FOR DIFFERENT TIME INTERVAL

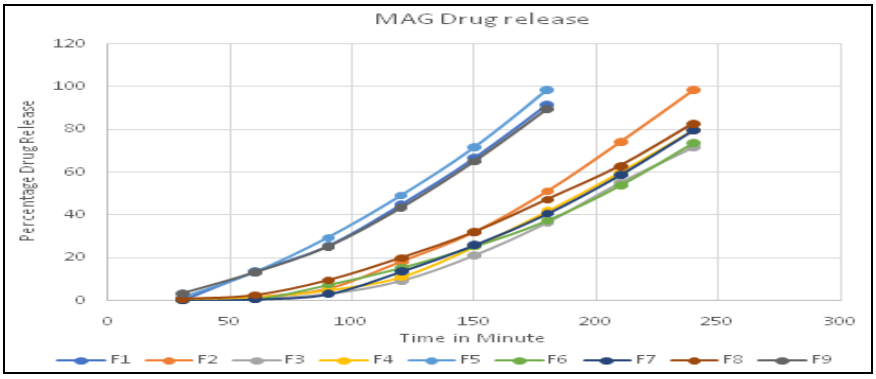
Time in Minutes	Formulation Number								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
30	5.199	0.94	0.23	1.42	1.40	0.78	1.559	0.26	6.73
60	11.91	4.42	2.57	4.62	11.74	3.38	4.24	2.65	15.0
90	22.02	9.77	8.45	12.13	26.40	8.84	10.03	7.41	28.67
120	35.43	18.25	18.28	19.98	44.53	17.47	17.99	15.89	46.77
150	52.15	33.56	29.09	30.72	67.91	28.41	28.65	28.60	68.24
180	71.15	52.30	42.63	45.25	92.33	42.06	41.99	44.74	92.34
210	92.63	74.27	58.57	62.23		58.05	58.10	62.96	
240		98.34	75.86	85.23		78.30	76.35	84.44	



GRAPH 1: %DRUG RELEASE OF QUERCETIN FROM DIFFERENT GEL FORMULATION FOR DIFFERENT TIME INTERVAL

TABLE 11: % DRUG RELEASE OF MAG FROM DIFFERENT GEL FORMULATION FOR DIFFERENT TIME INTERVAL

Time in Minutes	Formulation Number								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
30	0.093	0.6976	0.4651	0.543	1.40	0.232	0.116	0.68	3.48
60	13.6	1.744	1.16	1.75	13.37	0.78	0.814	2.48	13.37
90	25.58	5.465	3.25	4.96	29.53	7.44	3.14	9.45	25.34
120	44.76	18.13	9.302	11.09	49.18	15.34	13.6	19.92	43.48
150	66.39	31.97	21.16	25.11	71.62	25.34	25.93	32.01	65.11
180	91.39	51.16	36.51	41.7	98.6	37.44	40.58	47.36	89.65
210		74.3	55.11	59.99		53.87	58.72	63.1	
240		98.6	71.6	79.6		73.64	79.53	82.94	



GRAPH 2: %DRUG RELEASE OF MAG FROM DIFFERENT GEL FORMULATION FOR DIFFERENT TIME INTERVAL

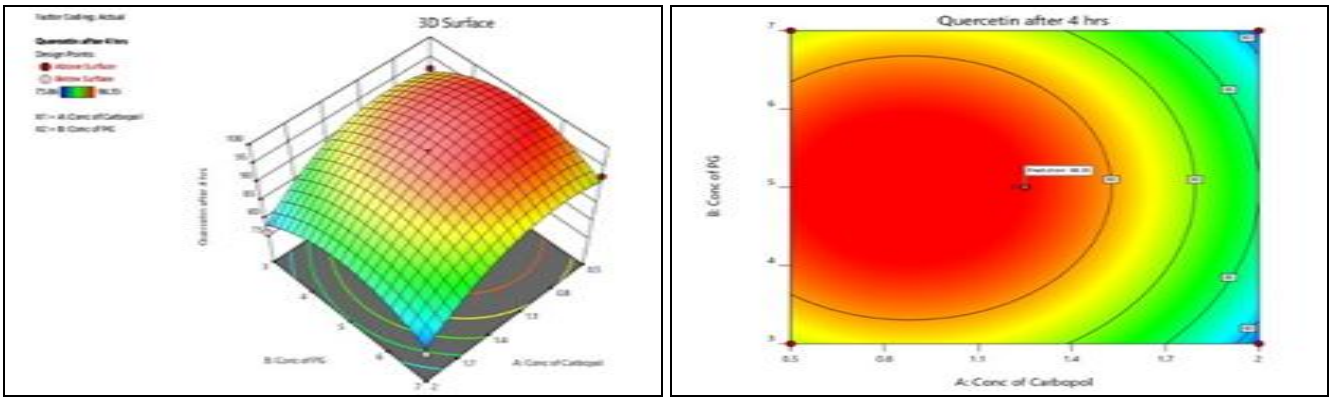


FIG. 3: 3D AND 2D PLOT FOR EFFECT OF CONC. OF CARBOPOL AND CONC. OF PG ON DRUG DIFFUSION OF QUERCETIN

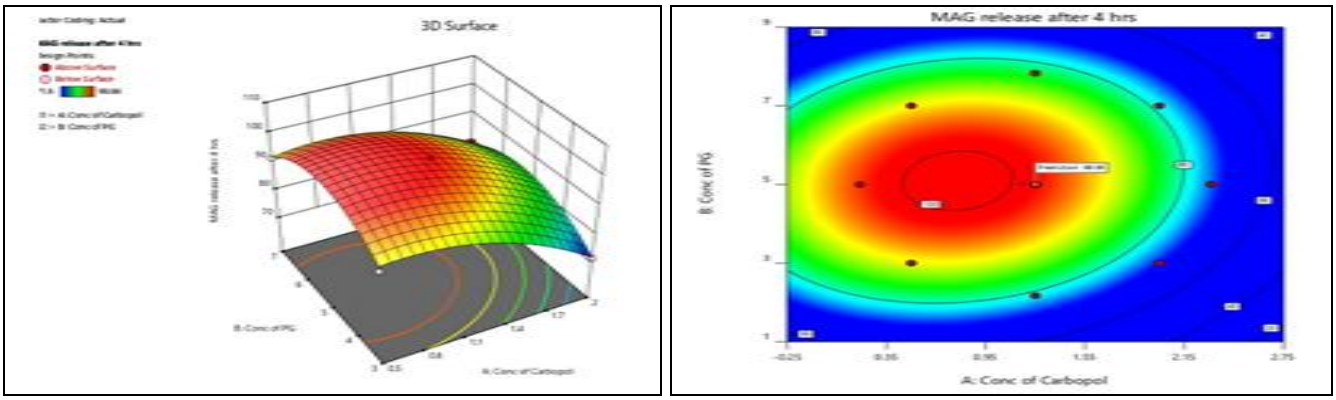


FIG. 4-3D AND 2D: PLOT FOR EFFECT OF CONC. OF CARBOPOL AND CONC. OF PG ON DRUG DIFFUSION OF MAG

Finalization of Batch: Selection of final batch depends on various evaluation parameters *e.g*., spred ability, *in-vitro* diffusion study.

After evaluation of the above parameters, we selected "F2" formulation, which shown the ideal property for gel.

Evaluation of Optimized Gel:

Texture Analyzer:

TABLE 12: TEXTURE ANALYZER FOR OPTIMIZED FORMULATION

Parameters	Result
Load at Target	55 g
Adhesive Force	20 g
Adhesiveness	0.7 mJ
Stringiness Work done	0.3 mJ
Cohesiveness	0.79
Springiness	0.292 cm
Gumminess	46 g

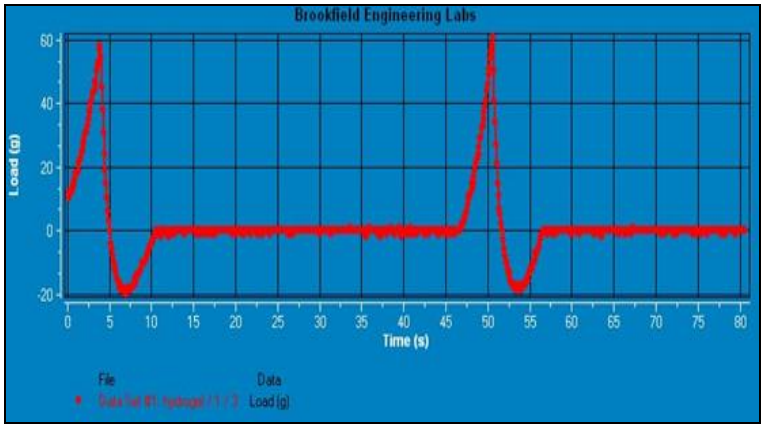


FIG. 6: TEXTURE ANALYZER OF OPTIMIZED FORMULATION (TIME (S) *VS* LOAD (G)

Viscosity:

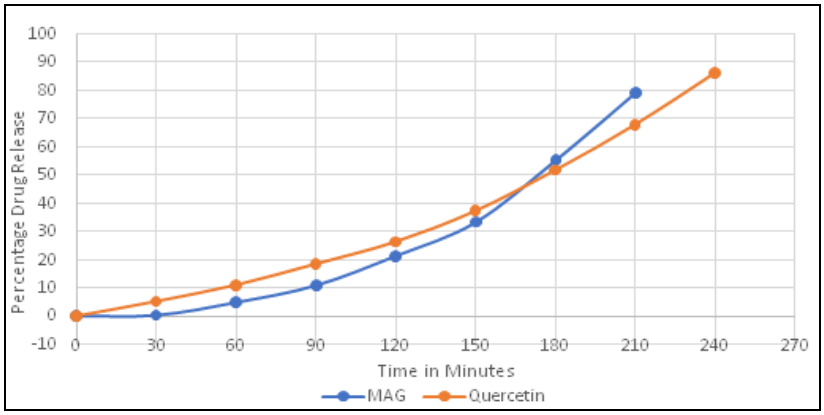
TABLE 13: VISCOSITY OF OPTIMIZED FORMU-LATION

RPM	1	2	3	Mean Viscosity (cP)	S.D
10	15236	15388	15306	15310	15310±78
50	10596	10750	10784	10710	10710±114
100	5100	5125	5090	5105	5105±20

Ex-vivo Drug Permeation Table 14, Graph 3:

TABLE 14: *EX-VIVO* PERMEATION OF QUERCETIN AND MAG THROUGH GOAT MEMBRANE OF OPTIMIZED FORMULATION

Time in Minutes	Cumulative % Drug Permeation Quercetin	Cumulative % Drug Permeation MAG
0	0	0
30	5.2253	0.2906
60	11.02253	4.825484
90	18.53553	10.872
120	26.38648	21.33711
150	37.38301	33.31386
180	51.83709	55.2906
210	68.03293	79.24409
240	86.38648	92.33



GRAPH 3: *EX-VIVO* PERMEATION OF QUERCETIN AND MAG THROUGH GOAT BUCCAL MUCOSA OF OPTIMIZED FORMULATION

Mucoadhesive Strength Determination Table 15:

TABLE 15: DETERMINATION OF MUCOADHESIVE STRENGTH OF OPTIMIZED FORMULATION (F2)

Formulation	1	2	3	Mean Strength	S. D
F 2	1784.59	1835.58	1759.1	1793.09	1793.09±42.48

Antimicrobial Study:

TABLE 16: DETERMINATION OF ANTIMICROBIAL ACTIVITY OF OPTIMIZED FORMULATION

Formulation	Microbial Diameter(mm)
F 2	10 ± 1
Marketed	15.667 ± 2.33

FIG. 7: DETERMINATION OF ANTIMICROBIAL ACTIVITY OF OPTIMIZED FORMULATION

Stability Testing Table 17, 18:

pH:

Table 17: pH of Optimized Gel (F2) for Stability Study at 5 ºC and 25 ºC

Time (Months)	pH at 5 ºC	pH at 25 ºC
01	7.02±0.19	7.06±0.170
02	7.1±0.2	7.18±0.180
03	7.23±0.11	7.27±0.090

Spreadability:

TABLE 18: SPREADABILITY OF OPTIMIZED GEL (F2) FOR STABILITY STUDY AT 5 ºC AND 25 ºC

Time (Months)	Spread Ability at 5 ºC	Spread Ability 25 ºC
01	3.67±0.27	3.49±0.19
02	3.57±0.05	3.39±0.25
03	3.59±0.010	3.46±0.391

Percentage Drug Content:

TABLE 19: % DRUG CONTENT OF OPTIMIZED GEL (F2) FOR STABILITY STUDY AT 5 ºC AND 25 ºC

Time (Months)	Drug Content of Quercetin at 5 ºC	Drug Content of Quercetin at 25 ºC	Drug Content MAG at 5 ºC	Drug Content MAG at 25 ºC
01	97.423±1.40	97.26±0.293	96.30±0.25	95.57±0.46
02	96.28±1.03	95.056±0.20	94.013±0.32	93.22±0.66
03	95.21±1.104	94.52±0.48	93.98±0.21	92.2±0.30

SUMMARY: The present work describes a study on "Formulation Development and Evaluation studies of Quercetin and MAG gels for the treatment of Mouth ulcer". The polymers, namely Carbopol-940, Propylene Glycol were used for the formulation of gels and studied for their drug release from the gel formulations. It is evident from the IR spectrum that all the polymers used in the gel formulations were compatible with the drug Quercetin and MAG. The calibration curve of Quercetin and MAG was performed in ethanol and Phosphate Buffer pH 6.8 which can be used for drug quantification in diffusion analysis. Different formulations of gel were prepared by using a varying concentration of Carbopol-940 and propylene glycol depending upon their range. Carbopol gels were non-greasy and smooth on application. Evaluation of gel involved (PH, Spreadability, Drug content, Drug diffusion). Evaluation of Final batch of gel involved (PH, Spreadability, drug content, Drug diffusion, Viscosity, Texture analyzer, Muco-adhesive strength, *ex-vivo* tissue permeation). In optimazation of Gel, F2 formulation was found better results compared to other formulation.

CONCLUSION: The present study of Quercetin and monoammonium glycyrrhizinate Gel increase patient compliance of gel and also to mask the test of quercetin with the help of sweet and pleasant test of Monoammonium glycyrrhizinate. The combination of Quercetin and MAG would be treating mouth ulcer Disease more effectively due to both drug shows activity and gives more benefits. Advantages of Quercetin and MAG combinational drug therapy doesn't have any serious side effect after for prolonged use and also maintain good bacterial flora of mouth which is important to minimizing ulcerative condition. Quercetin and MAG also has cardiovascular protection, anticancer, antitumor, anti-ulcer, anti-allergy, anti-viral, anti-inflammatory activity, anti-diabetic, gastroprotective effects, antihypertensive, immune-modulatory and antiinfective activity

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