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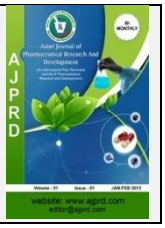

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Research Article

Formulation & Evaluation of Methotrexate and Triherbal Loaded Topical Emulgels for Anti-Arthritic Activity

Chandan Sah*, Dr. Sowjanya Battu, Deepak Prasad Yadav, Ajay Kumar Das, B. A. Vishwanath

Department of Pharmaceutics, Aditya Bangalore Institute of Pharmacy Education And Research Bengaluru- 560064

A B S T R A C T

Aim: The aim of this study was to prepare Methotrexate and triherbal loaded topical emulgels for anti-arthritic activity.

Methods: The above sources are subjected to soxhlation and aqueous and hydroalcoholic extracts of the above three will be prepared. The extracts will be prepared by proper maceration in suitable solvents in required proportions. The resultant extract will be converted into emulgel as follows: The gel portion of the emulgel will be made by dissolving carbopol-934 in cold water with constant stirring at a moderate speed until uniform mixture is obtained. The pH was then adjusted to 6–6.5 using triethanolamine (TEA). Tween 80 was dissolved in distilled water to prepare the aqueous phase of the emulsion while for the preparation of the oil phase of the emulsion; span 80 was dissolved in liquid paraffin. To preserve the emulsion, benzalkonium chloride was dissolved in water and the suitable amounts of extracts and methotrexate is dissolved in ethanol then both solutions are mixed with the aqueous phase. Both the aqueous and the oil phase were heated in a water bath at 70 °C separately. Then the oil phase was added drop wise to the aqueous phase with continuous stirring using homogenizer at speed of 3000 rpm for 10 min then cold to room temperature. At the end the gel and emulsion portions were mixed in 1:1 ratio with moderately stirring to prepare emulgel. The preparation is made viscous to be spreadable on the skin sufficiently without friction by trial-and-error way of mixing different proportions of gelling polymers. The formulation thus prepared is subjected to suitable characterization and evaluation studies and the optimized formulation is reported after obtaining results.

Results: Drug-polymer compatibility studies (FT-IR and DSC) showed no incompatibility between the drug and polymer. In- vitro permeation studies though egg membrane showed good drug release in the range of 78.91 to 98.92% over a period of 2 hours. The best formulation was found to be F3 showing in-vitro drug release of 98.92%. The correlation and coefficient (R2) values obtained from the kinetic equation shows the drug release from all the formulation (F1-F9) follow zero order drug release mechanism.

Conclusion: It can be concluded that Methotrexate and Triherbal loaded Topical emulgels could be a better formulation approach for Anti-arthritic activity.

Keywords: Topical emulgel, Methotrexate and Triherbal loaded, Anti-arthritic activity, Triethanolamine, Xantham gum,

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*Address for Correspondence:

Chandan Sah, Department of Pharmaceutics, Aditya Bangalore Institute of Pharmacy Education And Research Bengaluru- 560064

INTRODUCTION

Topical delivery can be defined as the application of a drug containing formulation to the skin to directly treat cutaneous disorders [e.g. acne, psoriasis] with the intent of containing the pharmacological or other effects of drug to the surface of the skin or within. Topical drug administration through various routes applied a wide spectrum of preparation for both cosmetic and dermatological, to their health and diseased skin. Topical preparations are applied to the surface of a part of the body and have effects only in a specific area of the body and are formulated in such a manner that the systemic absorption of the medicament is minimal. The most common examples of topical dosage forms are solutions, suspensions, emulsions, semisolids [e.g. powders and aerosols] among them ointments, creams, and lotions have numerous disadvantages.[1]

They are usually very sticky and cause uneasiness to the patient when applied moreover they also have less spreading coefficient and need to apply with rubbing. They also exhibit the problem of stability. Due to all these factors, a major group of semisolid preparation, transparent gel has expanded its use in both cosmetics and in pharmaceutical preparation. Inspite of many advantages of gels a major limitation is their inability an emulsion based limitation an emulsion based approach is being used so that a hydrophobic therapeutic moiety can be successfully incorporated and delivered through gels. When gels and emulsions are used in combined form the dosage forms are referred as emulgels.[2]

Emulgels

Emulgels are emulsions, either of the oil-in-water or water in oil type which are gelled by mixing with gelling agent. Emulsified gel is stable one and superior vehicle for hydrophobic or poorly water soluble drugs. In short emulgels are the combination of emulsion and gel.[3]

MATERIALS AND METHODS

Methotrexate was purchased from the Aarti drugs LTD, Mumbai, Coriandrum Sativum Extract, Cinnamomum Zeylanicum Extract, Withania Somnifera Extract was purchased from the Natural Remedies Pvt. Ltd. Triethanolamine, Methyl cellulose, Carbopol-934, Tween 80, were purchased from Yarrow chemicals, Karnataka. Span 80 purchased from Ghanshyam chemicals, Karnataka Benzalkonium chloride purchased from Indian fine chemicals, Karnataka. All the chemicals and reagents used in the study are of analytical grade.

Drug excipient compatibility studies

Fourier transforms infrared (FT-IR) spectroscopy

The infrared spectra of Methotrexate and other excipients was recorded using FT-IR spectrophotometer. The IR spectra of physical matrix were compared with that of Methotrexate to check for any possible drug – excipients interaction

Procedure

Emulgel is generally formulated in three steps which are:

- Preparation of the emulsion phase,
- Preparation of the gel phase, and
- Mixing the two phases for the formation of the emulgel.

For the preparation of aqueous phase Tween 80 was dissolved in distilled water while for the preparation of the oil phase of the emulsion; span 80 was dissolved in liquid paraffin. To preserve the emulsion benzalkonium chloride was added and the amount of methotrexate and triherbal extract was dissolved in ethanol.

Then both solutions were mixed with the aqueous phase. Both the aqueous and the oil phase were heated in a water bath at 70 C separately. Then the oil phase was added drop wise to the aqueous phase with continuous stirring using homogenizer (WiseStir HS-120A, Daihan Scientific, Korea) at speed of 3000 rpm for 10 min then cold to room temperatures to prepare o/w emulsion.

For the preparation of gel portion of the emulgel polymer (carbopol-934 and methyl cellulose) as mentioned in the formulation table was dissolved in water with constant stirring at a moderate speed until uniform mixture was made. The pH was then adjusted to 6–6.5 using triethanolamine (TEA). At the end the gel and emulsion portions were mixed in 1:1 ratio with moderately stirring to prepare emulgel.

Table 1: Formulation of methotrexate and triherbal loaded topical emulgels

Sl.no.	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
01.	Methotrexate (mg)	25	25	25	25	25	25	25	25	25
02	Coriandrum Sativum (mg)	1500	1500	1500	-------	-------	-------	-------	-------	-------
03	Cinnamomum Zeylanicum(mg)	-------	-------	-------	200	200	200	-------	-------	-------
04	Withania Somnifera(mg)	-------	-------	-------	-------	-------	-------	600	600	600
05	Liquid Paraffin (ml)	25	25	25	25	25	25	25	25	25
06	Distilled Water(ml)	25	25	25	25	25	25	25	25	25
07	Methyl cellulose (mg)	-------	500	-------	-------	750	-------	-------	1000	-------
08	Carbopol - 934 (mg)	-------	-------	500	-------	-------	750	-------	-------	1000
09	Triethanolamine (ml)	1	1	1	1	1	1	1	1	1
10	Span 80 (ml)	5	5	5	5	5	5	5	5	5
11	Tween 80 (ml)	5	5	5	5	5	5	5	5	5
12	Benzalkonium chloride(ml)	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
13	Distilled Water(ml)	Up to 100ml	Up to 100ml	Up to 100ml	Up to 100ml	Up to 100ml	Up to 100ml	Up to 100ml	Up to 100ml	Up to 100ml

Evaluation of Methotrexate and triherbal loaded topical Emulgels

1. Physical properties
2. pH determination
3. Spreadability
4. Centrifugation study
5. Rheological study
6. Swelling Index
7. Antibacterial activity
8. Drug content determination
9. In Vitro Drug Release Study
10. Stability Studies

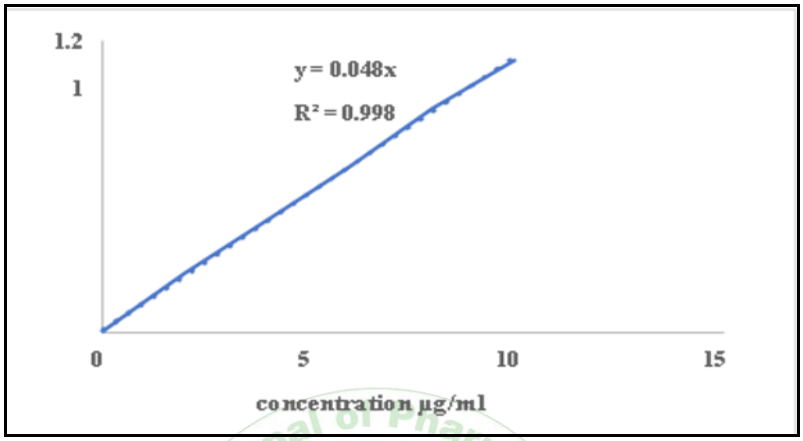

Figure 1: Standard plot of Methotrexate and triherbal extract

Table 2: Standard curve of Methotrexate and triherbal extract in 7.4pH phosphate buffer

Concentration (µg/ml)	Absorbance (298nm)
0	0.00±0.01
2	0.24±0.02
4	0.46±0.03
6	0.68±0.01
8	0.82±0.01
10	1.12±0.02

The value represents mean ± SD, n =3

Drug-excipients and drug- polymer compatibility studies

FT-IR Spectroscopy

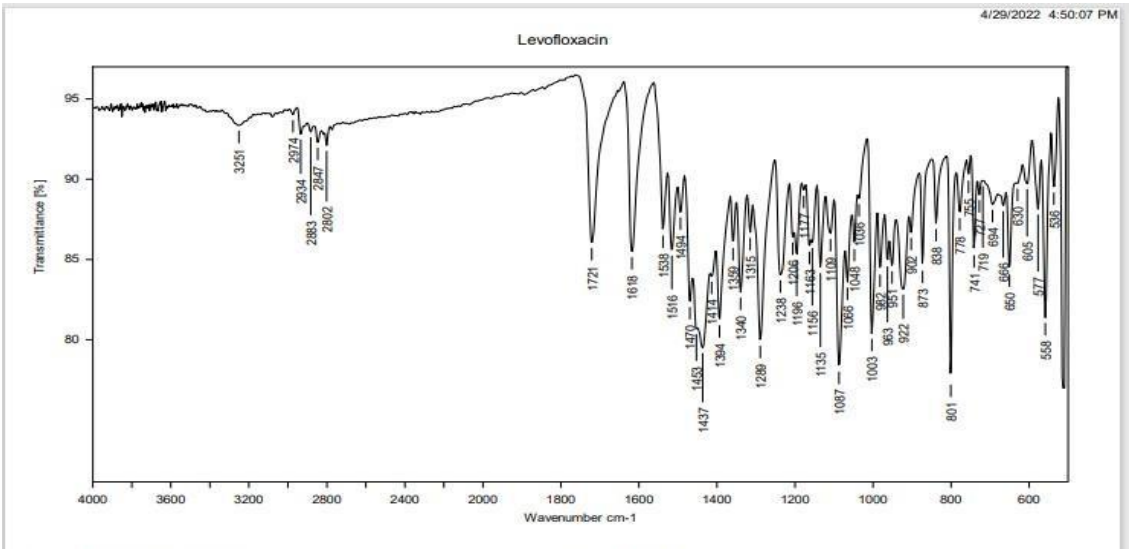

Figure 2: FTIR spectra of pure drug Methotrexate

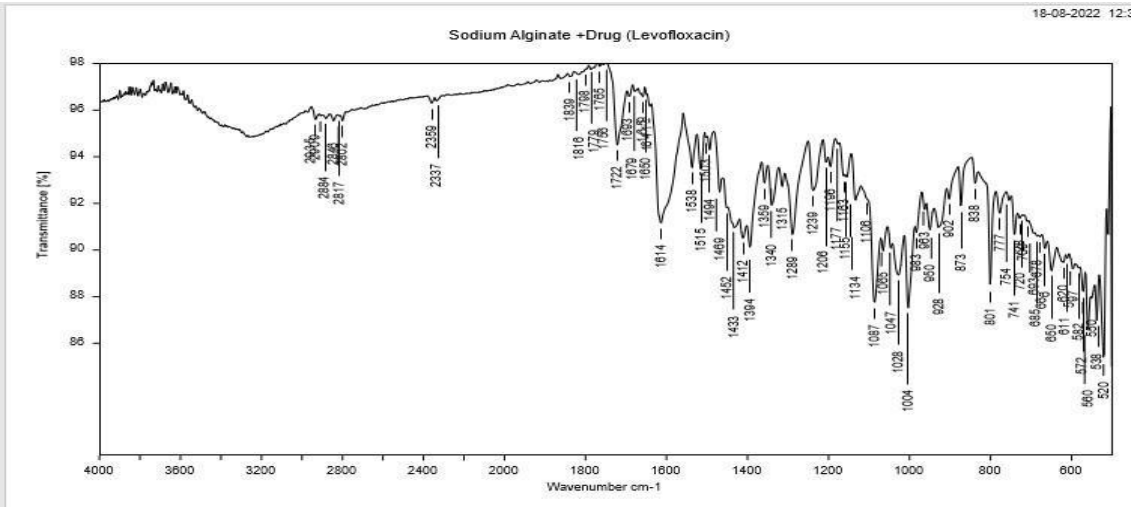

Figure 3: FT-IR spectra of pure drug Methotrexate + Triethanolamine

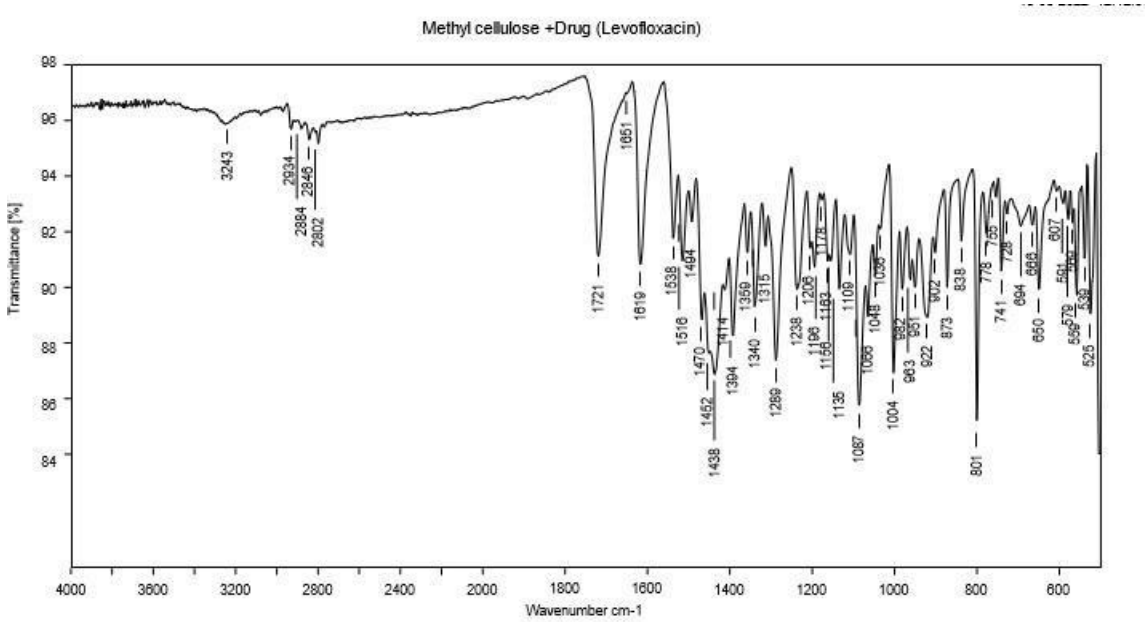

Figure 4: FT-IR spectra of pure drug Methotrexate + Methyl Cellulose

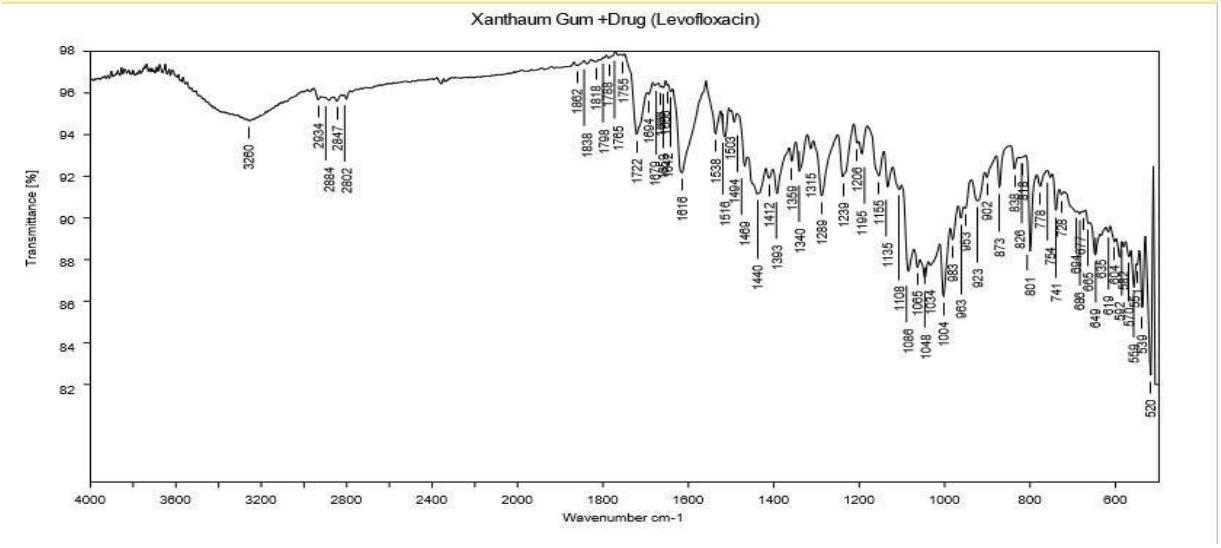

Figure 5: FT-IR spectra of pure drug Methotrexate + Carbopol - 934

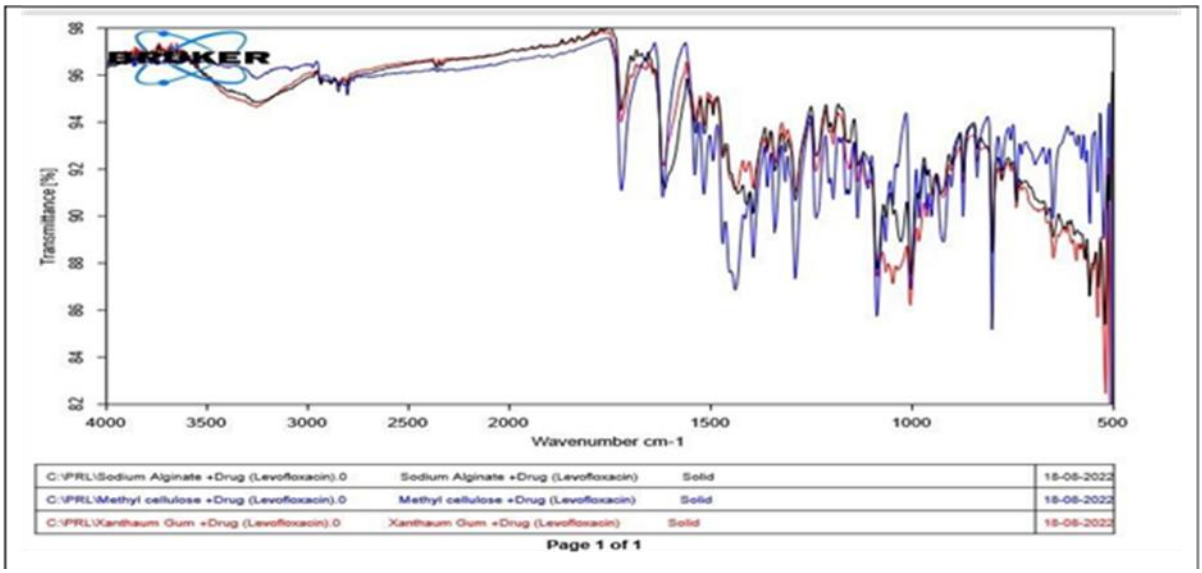

Figure 6: FT-IR characteristics peak of pure drug and excipients

Table 3: Interpretation of FT-IR

Groups(Cm^{-1})	Compound class	Methotrexate and trih extract	drug + Xantham gun	drug + Sodium alginate	drug + Methyl Cellulose
O-H stretching (3300-2700)	Alcohol	3251	3260	3262	3243
N-H stretching (3000-2800)	Amine salt	2846	2847	2846	2846
		2884	2882	2884	2884
		2934	2934	2935	2934
C=O stretching (1725-1700)	Ketone	1721	1722	1722	1721
C=O stretching (1620-1550/1420-1300)	Carboxylic acid	1619	1616	1614	1619
		1340	1340	1340	1340
		1359	1359	1359	1359
		1394	1393	1394	1394
C-N stretching (1555-1485)	Aromatic nitrocompounds	1516	1516	1515	1516
		1538	1538	1538	1538
O-H bending(1480-1395)	Carboxylic acid	1438	1440	1433	1438
		1452	1469	1452	1452
		1470	-	1469	1470
C-F stretching (1150-1000)	Fluro compound	1004	1004	1004	1004
		1087	1086	1087	1087
C-H bending (810-750 / 900-860)	Aryl 1,3- Disubstitution	778	778	777	778
		801	801	801	801
		873	873	873	873

Table 4: Melting point of methotrexate and triherbal extract

Trials	Results
1	**271 ºC**
2	**272ºC**
3	**271 ºC**
Average	**273 ºC**

Table 5: Solubility of methotrexate and triherbal extract

Solvent	Results
Tween 80	Freely soluble
Glacial acetic acid	Freely soluble
Water	Sparingly soluble

Table 6: Data for pH, Spreadability, Centrifugation, viscosity

Formulation code	pH	Spreadability in cn	Centrifugation	Viscosity ± SD in
F1	6.81±0.09	7.3±0.03	No separation	21,456±1.6
F2	6.81±0.09	8.2±0.06	No separation	24,576±1.7
F3	6.91±0.01	6.7±0.03	No separation	19,456±1.2
F4	6.75±0.06	7.6±0.03	No separation	22,746±1.3
F5	6.32±0.04	7.9±0.01	No separation	21,776±1.4
F6	6.72±0.03	6.8±0.03	No separation	19,976±1.5
F7	6.73±0.05	7.8±0.02	No separation	23,456±1.7
F8	6.52±0.04	8.3±0.01	No separation	21,786±1.3
F9	6.52±0.04	7.1±0.01	No separation	19,786±1.4

Table 7: Data for swelling index

Formulation	1st hour	2nd hour	3rd hour	4th hour	5th hour
F1	±25-0.01%	±37-0.02%	±49-0.01%	±56.5-0.02%	±69.3-0.01%
F2	±23.2-0.02%	±34.3-0.01%	±43.7-0.02%	±54.1-0.01%	±64.4--0.02%
F3	±20.6-0.01%	±29.6-0.03%	±31.9-0.02%	±53.6-0.02%	±63.7-0.01%
F4	±27-0.03%	±39-0.02%	±50.2-0.01%	±57.3-0.04%	±68.1-0.02%
F5	±22.9-0.03%	±35.4-0.04%	±44.1-0.02%	±54.9-0.03%	±65.3-0.01%
F6	±21.5-0.02%	±28.7-0.02%	±40.1-0.02%	±52.1-0.02%	±62.9-0.02%
F7	±27.5-0.01%	±40-0.01%	±51.5-0.02%	±58.1-0.01%	±69.5-0.01%
F8	±23.4-0.02%	±36.3-0.02%	±43.5-0.03%	±53.2-0.02%	±65.9-0.02%
F9	±20.1-0.02%	±27.6-0.01%	±42.1-0.03%	±53.9-0.02%	±63.6-0.02%

Table 8: Data for zone of inhibition of the Methotrexate and triherbal loaded topical emulgels

Formulations	Zone of inhibition in mm
F1	20mm
F2	19mm
F3	20mm
F4	16mm
F5	14mm
F6	14mm
F7	14mm
F8	18mm
F9	20mm
Methotrexate and triherbal loaded	18mm

Table 9: Data for drug content of Methotrexate and triherbal loaded topical emulgels

Formulation	Drug content
F1	81.1±0.60%
F2	91.8±0.44%
F3	90.3±0.52%
F4	89.3±0.15%
F5	83.8±0.47%
F6	82.8±0.44%
F7	91.3±0.32%
F8	92.1±0.39%
F9	91.7±0.41%

The value represents mean ± SD, n =3

Table 9: Data for Percentage cumulative drug release

Time in min	Percentage Cumulative Drug Release								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
15	13%	9%	8.91%	12.70%	14%	13.10%	9.6%	14.71%	13%
30	22.25%	20.15%	13.39%	25.21%	25.65%	33.33%	31.69%	24.43%	26.39%
45	24.75%	29.30%	32.44%	39.97%	38.90%	43.90%	43.31%	38.53%	38.03%
60	35.39%	35.51%	45.84%	48.37%	60.85%	50.66%	53.64%	50.84%	46.65%
75	47.92%	44.55%	54.67%	63.65%	79.39%	62.07%	65.89%	62.36%	58.89%
90	67.57%	53.59%	65.31%	73.87%	86.99%	70.02%	79.09%	74.89%	74.34%
105	81.45%	68.82%	82.05%	87.02%	95.34%	78.71%	87.49%	78.39%	77.85%
120	93.75%	78.91%	94.01%	98.2%	98.92%	85.08%	94.13%	82.65%	81.17%

The value represents mean ± SD, n =3

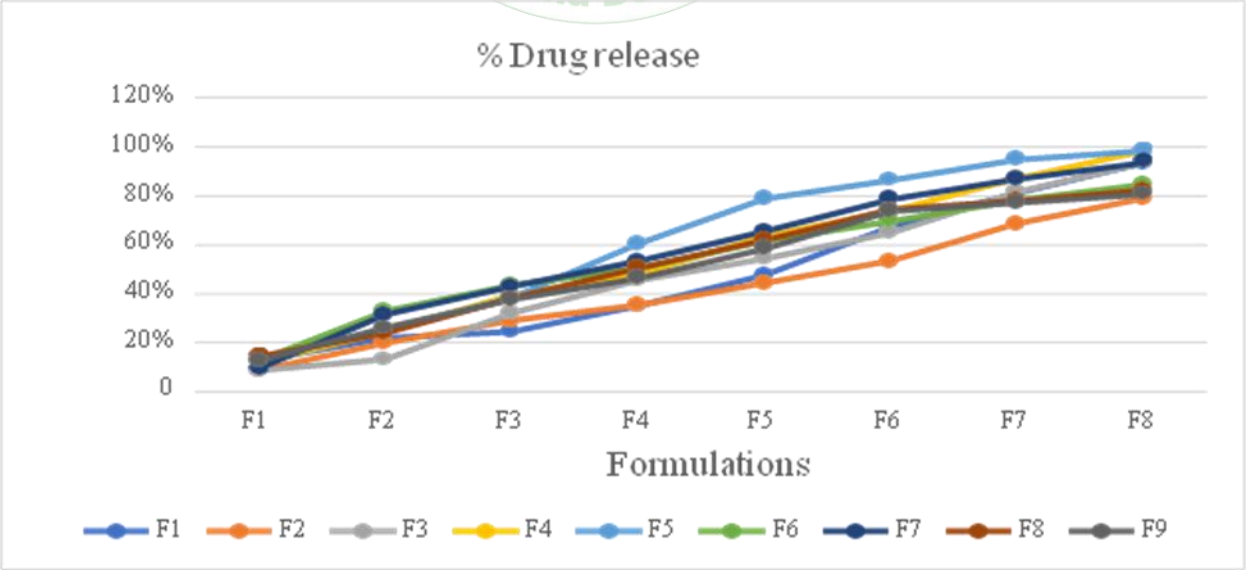

Figure: Cumulative % drug release of Methotrexate and triherbal loaded topical emulgels

Table 10: In-vitro drug permeation studies of formulation F3

Time in min	% Drug release
15	9.33±0.32
30	18.79±0.41
45	33.88±0.46
60	48.94±0.36
75	59.28±0.39
90	72.24±0.43
105	86±0.45
120	92.14±0.49

The value represents mean ± SD, n =3

CONCLUSION

- The topical emulgels of Methotrexate and triherbal loaded were prepared using various polymers such as methylcellulose, Carbopol - 934 and Triethanolamine. A total of nine different formulations were prepared. The following conclusions can be drawn from the results obtained.
- The FT-IR and DSC studies revealed that there was no chemical interaction of pure drug (Methotrexate and triherbal loaded emulgel) with the polymers and excipients.
- The Pre-formulation parameters like melting point, λmax, standard curve of all the formulations were found to be within the standard limits.
- The Post-formulation parameters like pH, spreadability, centrifugation, swelling index, viscosity, drug content, anti-bacterial activity of all the formulations were within the standard limits of official books.
- The pH of the F3 formulation was found to be 6.91 which ranges from 5.5 to 7. The swelling index of F3 was found that 63.7% which is in the range and it varies from 60%-76%. The spreadability of the F3 is 6.7cm and the values range should be between 1-9.333 Xantham under spindle 7 at 200 rpm was found 19,456±1.2cps and its range should be in between 18,000-30,000 cps. The anti-bacterial activity of topical emulgels showed zone of inhibition of 10mm.
- The formulation F3 selected for stability studies on the basis of their better and satisfactory evaluation parameters. Results showed there was not much variation in physical parameters even after the period of 90 days.
- From the results obtained it was concluded that, formulations F3 containing Methotrexate and Coriandrum Sativum found to be stable and retained their original properties during their study period.

SUMMARY

In the present work, an effort is made to formulate and evaluate triherbal loaded topical emulgels. Form the past two decades there is an enhanced demand for more patient compliance dosage forms. As a result, the demands for the technologies are increasing three folds annually. Since the developing cost of new chemical or drug molecule is very high, the pharmaceutical companies are focusing on development of new drug delivery systems for existing drugs with an improved efficacy and bioavailability together with reduced dose frequency to minimize side effects.

A. Pre-compression parameters were carried out to determine the flow properties of powder blend. Angle of repose, bulk density, tapped density, and carr's index were determined for all formulation which showed good result indicating good flow properties.

B. Post compression parameters were conducted for the powder blend. Swelling index, pH, rheological study, in-vitro dissolution study and drug content were conducted. The results of the evaluation parameters demonstrate that it is possible to design and develop triherbal loaded topical emulgels.

REFERENCES

1. Purushottam Sonaje Sumeet, Bhaskarrao Gondkar Sheetal, Bhandudas Saudagar Ravindra. Gellified Emulsion: A New Born Formulations For Topical Delivery of Hydrophobic Drugs A Review. World J. Pharmacy and Pharm Sci. 2013; 3(1):233-251.
2. Mohamad MI, Optimization of chlorphenesin emulgel formulation. The AAPS J. 2004; 6(3):1-5.
3. Shah A. Arpan, Kamdar Kamal, Shah Rushabh, Keraliya A. Rajesh. Emulgel: A Topical Prepartions for Hydrophobic Drugs. Ph. Tech Med. 2013; 2(5):370-376
4. Vats S, Saxena C, Easwari TS, Shukla VK. Emulsion Based Gel Technique: Novel Approach for Enhancing Topical Drug Delivery of Hydrophobic Drugs. IJPRS. 2014; 3(2):649-60.
5. Ravi KM, Teelavath M. Development and evaluation of polyherbal emulgel formulation. 2019; 19:1–9.
6. Nabarun Mukhopadhyay. Anti-arthritic Medicinal Plants: A Review, Res. J. Pharm. and Tech. 2019; 12(1): 375-381.
7. C.U. Rajeshwari, S. Siri, B. Andallu. Antioxidant and antiarthritic potential of coriander (*Coriandrum sativum* L.) leaves. e-SPEN J. 2013; 8(1):29.
8. Manjusha Choudhary. Medicinal plants with potential anti-arthritic activity. J. Intercult Ethnopharmacol. 2015; 4(2):147-179.