

Sardar Patel University

Vallabh Vidyanagar-388120

Final Report of the work done on the Inter Disciplinary Research Project

1. University Reference No. : G/No.DST Purse/12-13/1674
2. Period of report: From : 06/06/2012 to 31/03/2013
3. Title of Research Project: Hydrogel Thickened Microemulsion of Methotrexate for the Treatment of Psoriasis: Formulation and Clinical Implications
4. (a) Name of the Principal Investigator: Dr. Tapan R. Shah

(b) Deptt. Where work has progressed: Post Graduate Department of Pharmaceutical Sciences.
5. Effective date of starting the project : 08/08/2012
6. Grant Approved and expenditure incurred during the period of the report:
 - a. Total amount approved: Rs. 1,00,000/- (Rs. One lakh only)
 - b. Total expenditure Rs. Rs. 20,000/-
 - c. Report of the work done:
 - i. Brief objective of the project

Psoriasis is a quintessential chronic skin disorder known to affect a wide segment of population (nearly 2.5% of total world population) across the different age groups globally. Management of this disease requires knowledge regarding its occurrence, causative factors and behaviour of disease in different individuals.

Methotrexate is a folic acid antagonist with anti psoriatic as well as anti neoplastic activity. It is also effective in controlling recalcitrant psoriasis when administered by oral or parenteral route for long term. However, the systemic use of this drug unleashes number of adverse reactions including serious adverse reactions like hepatotoxicity. To reduce these systemic side effects, clinical studies with topical methotrexate have been undertaken for treating a plethora of cutaneous conditions and were approved by FDA in 1971 for treating severe psoriasis. However, one of the major limitations associated with currently available marketed preparation of methotrexate is limited diffusion and subsequent absorption of drug across the skin as it remains hydrosoluble and mostly in ionized form at physiological pH. One of the formulation strategies to enhance the penetration of drug across the skin in a non invasive manner is to formulate the drug in microemulsion based system.

b) Methodology adopted

To overcome the limitations of currently available topical marketed preparation of Methotrexate we hypothesized to design a methotrexate loaded microemulsion based delivery system that can be incorporated into hydrogel. The rationale underlying the said research work is to develop a user friendly, safe and efficacious topical microemulsion based gel for direct dermal application on psoriatic lesions. Microemulsions are clear, homogenous, isotropic systems composed of oily and aqueous phase incorporated with suitable surfactants and co surfactants. Formulating methotrexate in microemulsion based formulation is hypothesized to impart better penetration with the help of surfactant and penetration enhancers without any damage to skin. Nanometric globule size of microemulsions ensures intimate contact to the stratum Corneum facilitating drug delivery to skin layers. Microemulsion based system is also expected to provide with the sustained drug release of methotrexate reducing the dosage frequency and thereby, dose dependent adverse reactions.

Psoriatic skin loses its natural moisturizing capability and becomes scaly, so microemulsion was furthered thickened using aloe vera gel to impart moisturizing and protective effect it also helps in better and easy application to the affected areas by increasing contact time.

Objectives

- Preliminary screening of trials for selection of appropriate method Preparation of formulation by selected method.
- Establish methods for characterization of prepared formulation for solubility determination, drug excipients interaction.
- Formulation optimization
- Establishment of stability and reproducibility for optimized formulations.
- Checking the feasibility of scale up of optimized formulations.
- Clinical studies using patients suffering from chronic plaque psoriasis.

(iv) Methodology

(iv) Methodology in brief:

1. Pre formulation studies
2. Formulation development by water titration method.
3. Characterization of developed formulations by globule size measurement, zeta potential measurement, optical birefringence estimation, estimation of rheological parameters, in vitro diffusion studies.
4. Clinical evaluation of optimized formulation in patients of various age groups suffering from chronic plaque psoriasis.

(iv) b Methodology for Clinical Studies

It was planned that the optimized formulation of hydrogel thickened microemulsion containing methotrexate will be evaluated for its safety and efficacy by conducting clinical studies in 30 patients of 18-60 years age group (approved by hospital ethics committee of Prmaukhswami Medical College, Karamsad and after obtaining written consents from the concerned patients); with psoriatic lesions occupying not more than 20% body surface area. The study was intended to be undertaken for a period of 12 weeks.

Subject Recruitment Procedure

The study was planned so as to include all the patients attending to skin OPD with complaint of clinical feature suggesting psoriasis.

A. Inclusion criteria:

All new and existing cases of psoriasis diagnosed at the skin OPD.

B. Exclusion criteria:

Patient who are not ready for the study.

Patient with past history of hepatotoxicity or renal disease.

Pregnant or lactating women.

Informed Consent

Informed consent was taken from patient for detailed clinical examination and photographs as per prescribed format.

Detailed Methodology of the clinical study:

The optimized formulation of hydrogel thickened microemulsion containing methotrexate will be evaluated for its safety and efficacy by conducting clinical studies in 30 patients of 18-60 years age group (approved by hospital ethics committee and after obtaining written consents from the concerned patients); with psoriatic lesions occupying not more than 20% body surface area. The study is intended to be undertaken for a period of 12 weeks.

Comparative studies are to be conducted in which formulation developed in our laboratory (designated as test product) will be evaluated for its efficacy by comparing it against commercially available gel based formulation of methotrexate, (coded as marketed formulation) or simple gel incorporated with methotrexate prepared in our lab (coded as standard product).

Besides, we are planning to make following observations:

Time required to heal external lesion and any other effects will be evaluated periodically.

At the end of study laboratory tests including complete blood count, serum creatinine and liver function tests will be performed.

Patients will also be evaluated for systemic as well as topical side effects so as to establish the safety and efficacy of newly developed microemulsion based formulations.

Plan of Statistical Analysis

Analysis of data will be done depending on the variables, according to the applicable parameters.

Study design: observational study

[Cross sectional study]

Chi square test, ANOVA.

d. Results and Conclusion

The studies are ongoing and on completion will be subjected to data compilation and appropriate conclusion will be drawn.

e. Details of publications (including conference presentation)

We have avoided publishing/presenting the data since we are planning to file a patent application based on the basis of final findings of the ongoing clinical study. Due to irregularity of patients and an issue of therapy discontinuation by patients, the project could not be completed within said deadline. The results obtained so far seem to be promising and we are planning to file at least a provisional patent application and hence, have refrained from presenting/publishing the data.

iii. Has the progress been according to original plan of work and towards achieving the objective, if not, state reasons.

The progress of work has been in accordance with prepared work plan and methodology. However, we are facing some issues in clinical evaluation of the prepared formulation. The formulation development was successfully ventured out by the Department of Pharmaceutical Sciences followed by the clinical evaluation of the product in psoriatic patients at Skin and V.D. department, Pramukhswami Medical College, Karamsad.

However, we have been facing some issues regarding the irregularities on patients' side, non adherence to the therapy, discontinuation of therapy by the patients etc. and hence, we could not conduct the trials in sufficient number of patients and consequently, could not generate the required data till the deadline of this project. Though the hospital authorities at Karamsad Medical college have been extremely supportive and co operative, premature and abrupt therapeutic discontinuation without informing/consulting the doctors is a common practice adopted by patients and much less can be done to address this issue. However, we are trying to overcome this lacuna and redress the same. Nonetheless, the matter can be solved over the period of couple of

months. Hence, we request the University authorities to kindly extend the financial help and timeline of the project till 31st March, 2014 so that we can complete the studies as per the scheduled plan and can generate the data that can be published/patented.

iv. Please indicate the difficulties in implementing the project:

Non consented therapeutic discontinuation by the patients has resulted in delay in completion of the project. The project has promising potential and can prove to be of immense utility in developing the topical products of methotrexate in management of Psoriasis, however, we could not get sufficient number of patients enrolled for the therapy as well as those who were recruited, discontinued the therapy without consultation/information. Patient non adherence and high attrition rates are the major obstacles we have been facing in the project.

v. If project has not been completed, please indicate the reasons:

Same as cited above.

vi. Any other information which would help in evaluation of work done on project
In spite of the technical issues faced by us in terms of patient withdrawal from the therapy, we would try to resolve the issue and try to get the things on track. However, we request the University authorities to kindly extend the financial assistance and timeline of the project upto 31st March, 2014 so that we can resolve the issue in meantime.

Date: 12/04/2013

Signature of the Principal Investigator

R.V.VOZ

Signature of the Co Investigator

[Signature]
Head of the Department
I/C Head
Post Graduate Department of
Pharmaceutical Sciences
Sardar Patel University,
Vallabh Vidyanagar Pin 388 120.

FORWARDING LETTER

Phyrmu / 2012-13/207

Date: 12/04/2013

To,
The Development Officer,
Sardar Patel University,
Vallabh Vidyanagar.

Inward No.: 991
Section: Gen
Date: 1-5-13

SUB: a) Submission of Final Report on Inter Disciplinary Project in Science.
b) Extension of the deadline of the project till 31st March, 2014.

Dear Sir,

With reference to letter (G-1/Interdisciplinary/DST PURSE/273), I, undersigned (Dr. Tapan R. Shah) am submitting the Final Report on Inter Disciplinary Research Project entitled: "Hydrogel Thickened Microemulsion of Methotrexate for the Treatment of Psoriasis: Formulation and Clinical Implications" (Grant No. G/No/DST PURSE/12-13/1674, dated: 06/06/2012).

I am submitting the detailed report as per the prescribed format for further process.

However, we would like to present a joint request in the capacity of P.I. and Co Investigator of the project to kindly extend the budget utilization and deadline for the said project till 31st March, 2014 as due to drop out of psoriatic patients.

Kindly accept the same and do the needful.

Thanking you,

Yours Sincerely,

Tapan Shah

Dr. Tapan R. Shah,
(Principal Investigator),
Asst. Professor in Pharmaceutics
Post Graduate Department of Pharmaceutical Sciences,
Sardar Patel University,
Vallabh Vidyanagar.

R.V. Vora

Dr. Rita V. Vora
(Co-Investigator),
Professor and Head,
Skin and VD Department,
P.S. Medical College,
Karamsad.

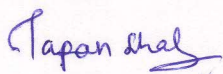
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I/C Head
Post Graduate Department of
Pharmaceutical Sciences
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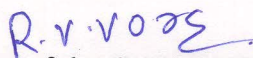
Utilization Certificate

Certified that the grant of Rs. 1,00000/ (Rupees one lakh only) received from the University under the scheme of support for Interdisciplinary Research Project entitled: "Hydrogel Thickened Microemulsion of Methotrexate for the Treatment of Psoriasis: Formulation and Clinical Implications". Vide University letter No. G/No.DST Purse/12-13/1674 dated 06/06/2012 has been partially utilized for the purpose for which it was sanctioned and in accordance with terms and conditions laid down by the University.

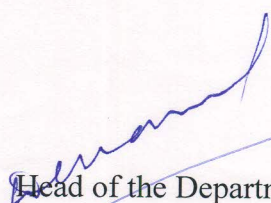
Date: 12/04/2013



Signature of the Principal Investigator



Signature of the Co Investigator


Head of the Department
I/C Head
Post Graduate Department of
Pharmaceutical Sciences
Sardar Patel University,
Vallabh Vidyanagar Pin 388 120.

Sardar Patel University
Vallabh Vidyanagar- 388120

Statement of Expenditure in Respect of Inter Disciplinary Research Project

1. Name of the Principal Investigator: Dr. Tapan R. Shah
2. Department: Pharmaceutical Sciences
3. University Approval No and Date: G/No.DST Purse/12-13/1674 dated 06/06/2012
4. Title of the project: "Hydrogel Thickened Microemulsion of Methotrexate for the Treatment of Psoriasis: Formulation and Clinical Implications".
5. Effective date of starting of the project: 08/08/2012
6. A. Period of Expenditure: from 08/08/2012 to 31/03/2013.

b. Details of Expenditure

Sr. No.	Item	Amount Approved (Rs.)	Expenditure Incurred (Rs.)
1.	Books and Journals	N.A.	
2.	Equipment	N.A.	
3.	Contingency	80,000	7,000
4.	Field work/travel	3,000	1,000
5.	Hiring Services	5,000	
6.	Chemicals and Glassware	12,000	12,000
7.	Overhead	N.A.	
8.	Any other items	N.A.	
9.	Total	1,00,000/-	20,000/-

1. It is certified that the purchase and expenditure have been made in accordance with the terms and conditions laid down by the University.
2. It is certified that the grant of Rs. 1,00,000/- (Rupees one lakh only) received from the University under the scheme of support for Interdisciplinary Research Project entitled: "Hydrogel Thickened Microemulsion of Methotrexate for the Treatment of Psoriasis: Formulation and Clinical Implications". Vide University letter No. G/No.DST Purse/12-13/1674 dated 06/06/2012 has been partially utilized for the purpose for which it was sanctioned and in accordance with terms and conditions laid down by the University.

Date: 12/04/2013

Signature of the Principal Investigator

Signature of the Co Investigator

Head of the Department

I/C Head
Post Graduate Department of
Pharmaceutical Sciences
Sardar Patel University,
Vallabh Vidyanagar Pin 388 120.

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Statement of Expenditure Incurred on Field Work

Name of the Principal Investigator: Dr. Tapan R. Shah

Name of the place visited	Duration of visit		Mode of journey	Expenditure (Rs.)	Purpose of the visit
	From	To			
Pramukhswami Medical College, Karamsad	08/082012	31/03/2013	Private two wheeler	1,000	Supplying formulation samples for clinical studies, routine patient follow up and reporting

Certified that the above expenditure is in accordance with the University norms for interdisciplinary research project

Date: 12/04/2013

Tapan Shah

Signature of the Principal Investigator

R. V. V. 02

Signature of the Co Investigator

[Signature]
Head of the Department
I/C Head

Post Graduate Department of
Pharmaceutical Sciences
Sardar Patel University,
Vallabh Vidyanagar Pin 388 120.

REPORT ON CLINICAL STUDY

Sr.No.	Details of Patient		Treatment	PASI at the time of admitting the Patient (with date)	PASI index observed after treatment with	Remarks
	Gender	Age (years)	MTX G ₁ /G ₂		MTX G ₁ /G ₂	
1	Male	44	MTX G ₂	2.4 (23/2/13)	N.A.	Patient dropped out
2	Female	55	MTX G ₁	2.8 (21/12/12)	2.0 (6/2/13)	Reduction in PASI
3	Male	35	MTX G ₂	28.8 (31/12/12)	N.A.	Patient dropped out
4	Male	78	MTX G ₁	14.7(31/12/12)	N.A.	Patient dropped out
5	Female	35	MTX G ₂	14.4 (26/12/12)	N.A.	Patient dropped out
6	Female	50	MTX G ₂	7.7 (19/12/12)	N.A.	Patient dropped out
7	Male	59	MTX G ₂	8.6 (23/11/12)	N.A.	Patient dropped out
8	Male	27	MTX G ₁	5.0 (19/11/12)	N.A.	Patient dropped out
9	Male	70	MTX G ₁	7.2(12/10/12)	N.A.	Patient Discontinued
10	Male	46	MTX G ₂	5.8 (3/8/12)	Almost nil (29/11)	Psoriasis cured after completion of therapy
11	Male	59	MTX G ₁	3 (27/7/12)	Reaction after application	Discontinued due to reaction
12	Male	56	MTX G ₂	4.2 (29/8/12)	N.A.	Patient discontinued
13	Female	56	MTX G ₂	11 (3/8/12)	N.A.	Patient Discontinued
14	Female	26	MTX G ₂	1.3 (11/8/12)	N.A.	Patient discontinued

Discussion:

The results of the studies conducted in 14 patients over the span of time of 6 months (October 2012 to March 2013) indicated improvement in psoriatic patient treated with the topical formulation of Methotrexate (as indicated in Patient No. 10 treated with MTXG₂) however,

we would be able to establish the promising potential of proposed formulation in successful clinical management of Psoriasis only after completion of elaborate studies for some additional time period (till **31st March, 2014**).

One of the major constraints faced by us in the current investigation is consistent drop out of the patients and non-consented discontinuation of the therapy by the patient that led to insufficient data compilation. Drop out of patient may also be attributed to improvement in patient's condition which might have induced patient to discontinue the therapy. However, it is too early to arrive at such a conclusion and the actual reasons for patient drop out need to be established and redressed subsequently.

Hence, a strategy has been jointly worked out by the P.I. and Co-Investigator to address the issue and we jointly seek the kind consent of University authorities to allow us to **extend the study for additional one year (till 31st March, 2014) so as to collect the sufficient data that can be published or processed further**. Since, the budget also remains underutilized; the studies can be further continued and afforded with unused grant. Sincere efforts will be undertaken to improve patient adherence to therapy and reduce patient drop out by identifying the cause of patient drop out and work out the remedial measures to redress the same and work towards the successful outcome.