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Review article

Formulation and evaluation of dapsone loaded microsphere incorporated gel delivery system

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ABSTRACT

The present study was aimed to control and prolong the release of Dapsone by formulating and microspheres and incorporating in to gel dosage form for topical application with a reduced frequency of application and hence lesser known side effects. The microspheres were prepared using suspension polymerization method. An increase in concentration of the polymer was found to increase the particle size along with the amount of entrapped drug. The surface of the microspheres was found to be smooth. In vitro drug release of microspheres exhibited a biphasic release pattern with an initial burst release effect. The release kinetics data best fitted with first order kinetics and the Higuchi matrix data was able to explain the controlled release of drug from the microspheres. The gel formulations made from the microspheres (DM4, (drug: polymer, 1:4)) possessed all the physicochemical evaluation parameters within acceptable limits. The in vitro diffusion data made it evident that the gel formulation with 1.0% HPMC, loaded with DM4 was able to release about 68% drug at the end of 24 hours.

Keywords: Microspheres, Dapsone, Gel, Franz-diffusion cell, Chitosan, suspension-polymerization.

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INTRODUCTION

Controlled release drug delivery systems have continuously addressed many of the shortcomings associated with traditional methods of administration. Controlled release drug delivery utilizes polymer-based disks, pellets, or microparticles that have the capacity to encapsulate drug and release it at predetermined rates for relatively longer periods of time and other advantages like drug shielding and improved patient acceptability [1,2]. It has been provent that drug concentrations can be controlled through coupling the desired drug to liposomes, microparticles or nanoparticles. Drug encapsulation within microparticles (1-1000 µm) and nanoparticles (1-1000 nm) is typically achieved with biodegradable and biocompatible polymers [1].

Dapsone is a sulfone antibacterial agent acting by competitive inhibition of the enzyme necessary for the synthesis of folic acid. The use of oral dapsone in acne is limited by the potential for adverse effects and hence it is restricted to topical use in the management of acne vulgaris [3]. The side effects on topical application include erythema, dryness, oiliness, and skin peeling which could be reduced by using dapsone topical preparations on alternate days. The alternate day use of anti acne preparation therefore reduces the efficacy of the product in reducing the visual lesions. Previously attempts have been made many a times for controlling the release of Dapsone by designing of various delivery systems employing different strategies [4-10]. It is a well-known fact that polymeric microspheres and micro sponges have the capacity to improve the stability of incorporated drug molecules and prolong the release of incorporated drugs [11]. Hence it was envisioned that incorporating Dapsone in polymeric microparticles and formulating them as gels would enable in improved stability and prolonged duration of action of the gel thereby reducing the topical side effects associated with the topical preparations of Dapsone.

MATERIALS AND METHODS

The drug (Dapsone) was purchased from Yarrow Pharmaceuticals, Mumbai. All other reagents and Chemical used were of analytical grade and procured from the local suppliers of Oxford fine chemicals, CDH, Rankem and HiMedia.

Standard calibration curve of Dapsone

Accurately weighed drug (10 mg) was transferred into clean and dried 100 mL volumetric flask and dissolved in minimum quantity of methanol. The volume was made up to 100 mL with the solvent system methanol-water (60:40) [12]. Dilutions of 20-100 µg/mL were prepared. The solutions were filtered through Whatman filter paper and absorbance of the filtrate was measured at 295 nm using UV-visible spectrophotometer. A graph of concentration v/s absorbance was plotted.

Formulation of Microspheres of Dapsone

Chitosan microspheres of Dapsone were prepared by a suspension polymerization technique using glutaraldehyde as the cross-linking agent as per reported method [13] with slight modifications. Weighed amount of chitosan was dissolved in 10 ml water and the required quantity of Dapsone (table 1) was uniformly dispersed throughout it, as the internal phase. This dispersion was added drop-wise to 50 ml sesame oil as the external phase with continual stirring using an overhead stirrer at 1000 rpm. 20 ml glutaraldehyde saturated toluene solution was then added to it for hardening the microspheres. The cross linked and hardened microspheres were washed with acetone, separated by filtration and dried overnight. Five different formulations with drug: polymer ratios were prepared.

Table 1: Formulation microspheres using Chitosan

Formulation Code	Dapsone: Chitosan
DM1	1:1
DM2	1:2
DM3	1:3
DM4	1:4
DM5	1:5

EVALUATION OF MICROSPHERES

Surface morphology (SEM)

Scanning electron microscopy has been used to determine surface topography, texture, and to examine the morphology of the particles.

Particle size and frequency distribution analysis

Determination of the average particle size of Dapsone loaded microspheres was carried out by optical microscopy using a stage micrometer and calibrated eye piece. A small quantity of Dapsone microspheres was spread on a clean glass slide and the size of 300 particles was determined for each formulation batch.

Determination of Drug Content

The amount of Dapsone associated with microspheres was assessed in terms of the surface drug and entrapped drug.

Surface Drug

A suspension of an accurately weighed amount of Dapsone microspheres (50 mg) in methanol was sonicated at 125 W for 4 min. The suspension was then centrifuged at 3000 rev/min for 3 min. The supernatant was analyzed using UV visible spectrophotometer as described in calibration curve at 295 nm. Again, the microspheres were treated with methanol in the above manner two more times. The second and third washings were also were analyzed for the Dapsone content to obtain the total amount of Dapsone adsorbed on the surface of microspheres.

Entrapped Drug

The microspheres obtained after three washings with methanol were digested in a small quantity of trichloroacetic acid and methanol (2 ml each). The digested homogenate was centrifuged at 3000 rev/min for 10 min, and the supernatant was assayed for Dapsone content using UV visible spectrophotometry method at 295 nm.

In Vitro Drug Release Study

To study the rate and extent of drug release from the microspheres, dissolution of Dapsone loaded microspheres was studied using USP dissolution test apparatus. An accurately weighed sample of microspheres equivalent to 25 mg of Dapsone was placed in 900 mL of phosphate buffer pH 7.4 and was subjected to dissolution with a paddle speed of 150 rpm at 37 ± 0.5°C. Aliquots (5 mL) were withdrawn at 1, 2, 4, 10 and 24 h and were assayed spectrophotometrically at 295 nm. The percentage of drug released at various time intervals was calculated and plotted against time [14,15].

Gel Formulation of Dapsone loaded Microspheres

The accurately weighed quantity of the Dapsone microsphere (table 2) was dispersed in purified water with constant stirring and the dispersion was heated to 50°C. The designated amount of HPMC was added to the solution under continuous stirring while maintaining the temperature at 50°C to ensure no air entrapment. The dispersion of the gelling agent was neutralized using 10% NaOH solution to neutral pH and the stirring was continued to obtain a gel [16].

Table 2: Formulation of Dapsone microsphere incorporated Gel

Ingredient	Batch formula for 100g gel		
	DMG1	DMG2	DMG3
Dapsone Microsphere (g)	5.0	5.0	5.0
HPMC	0.5	1.0	1.5
10% NaOH (mL)	QS	QS	QS
Water (mL)	98.5	98.0	97.5

Evaluation of Dapsone microsphere incorporated Gel [17,18]

The prepared gel formulations were evaluated for official and non official specifications.

pH and viscosity of the formulation

Accurately weighed quantity of 5 g of each gel formulation was mixed separately with 45 mL of distilled water and the pH of the solution was determined with the help of digital pH meter. The viscosity of each formulation was measured at 10 rpm by using Brookfield DV-1 viscometer employing a S94 spindle.

Spread ability and Homogeneity

Spread ability of the gel was evaluated using Arvouet-Grand Method by placing 1 g of the gel formulation between two glass plates of 20 X 20 cm and placing a weight of 125 g on the top plate. The diameter of the formulation was recorded as an index of spread ability. All the gel formulations were evaluated for homogeneity by visual inspection after the by observing for their appearance and presence of any aggregates.

Drug content

100 mg of gel was dissolved in 100 mL phosphate buffer pH 7.4 and shaken using a mechanical shaker for 2 h to dissolve the

contents completely. The solution was then filtered and the drug content was determined spectrophotometrically at 295 nm using a blank solution (phosphate buffer pH 7.4).

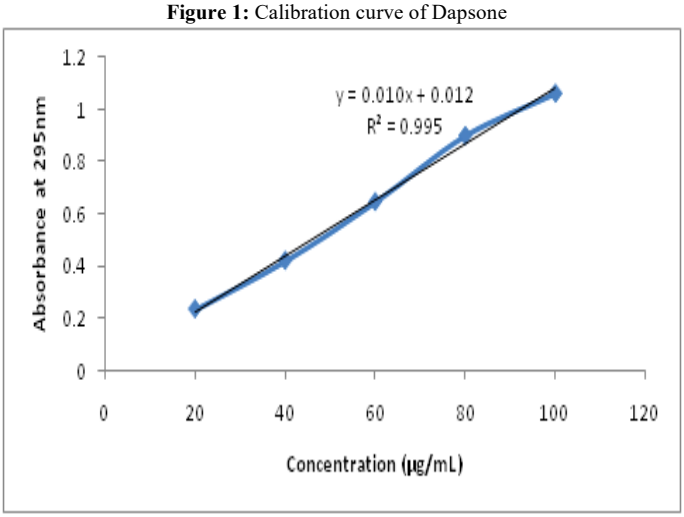
In vitro diffusion of Dapsone from Gel [19]

In-vitro drug diffusion study of all gel formulations were performed by using Franz-diffusion cell. Freshly peeled egg membrane was placed between the receptor and donor compartment of the Franz-diffusion cell. The receptor compartment contained 10 mL of phosphate buffer pH 7.4, maintained at 37 ± 1°C. The assembly was fixed up on a magnetic stirrer. 0.1 g quantity of gel sample was placed over the egg membrane and solution of phosphate buffer pH 7.4 in the receptor compartment was stirred continuously using magnetic bead at 50 rpm. Samples of 1 mL were withdrawn at 1, 2, 4, 10, 12 and 24 h and diluted with 10 ml of blank solution (phosphate buffer, pH 7.4) and analyzed using spectrophotometer at 295 nm.

RESULTS AND DISCUSSION

The standard calibration curve of Dapsone was obtained by measuring the absorbance of appropriately diluted stock solution at 295 nm in the solvent system (methanol: water; 60:40) and plotting the graph of absorbane v/s concentration (figure 1).

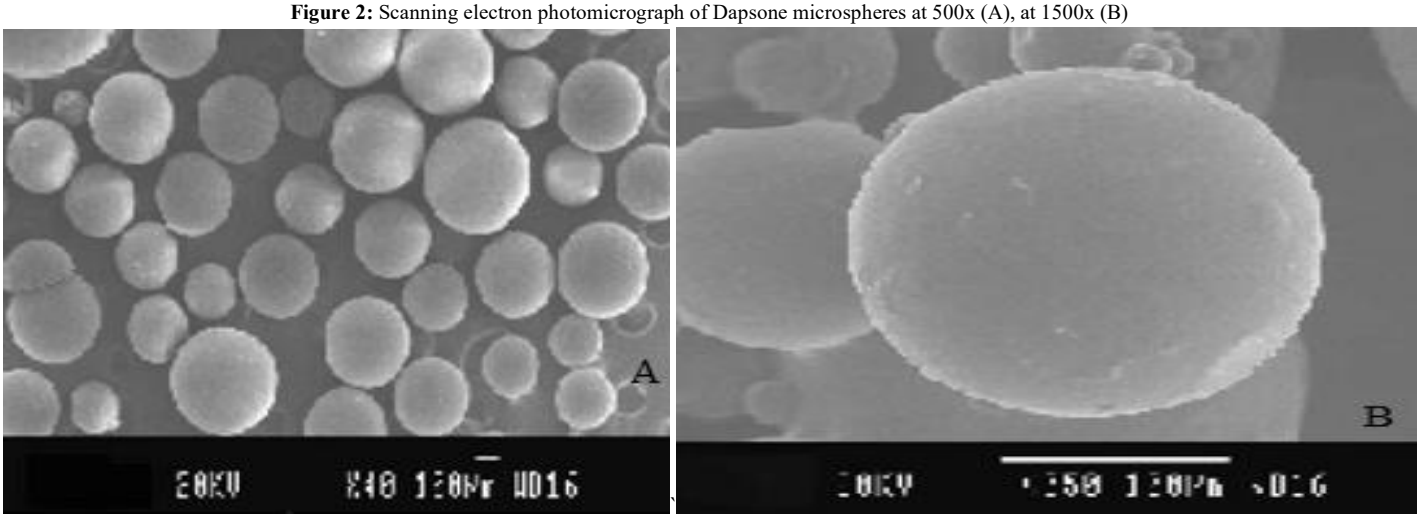
Figure 1: Calibration curve of Dapsone



Surface Morphology (SEM) of microspheres

The surface morphology of the Dapsone microspheres was studied by SEM. The SEM photographs of the formulations are shown in figure 2.

Figure 2: Scanning electron photomicrograph of Dapsone microspheres at 500x (A), at 1500x (B)

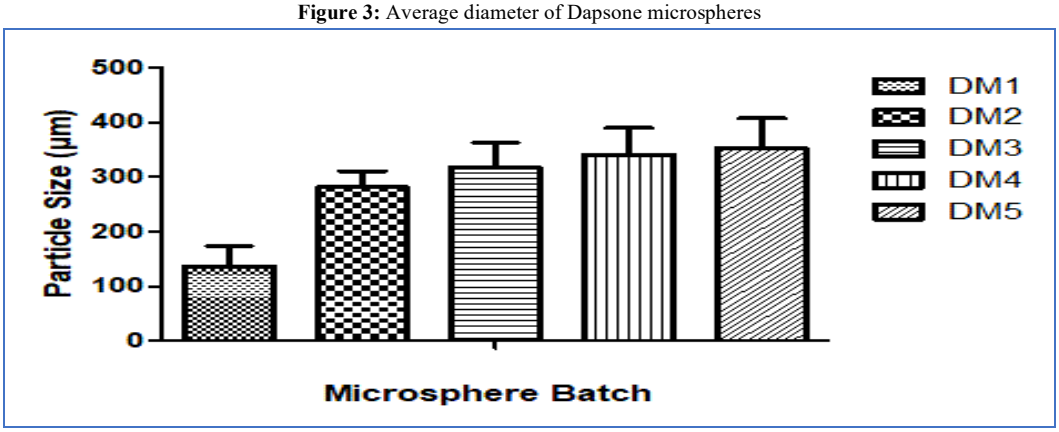


The surface of the microspheres was smooth and crosslinked and the microspheres formed were spherical in shape as shown in the photomicrographs.

Frequency distribution analysis and particle size

The particle size of the microspheres was determined using stage micrometer and is represented in figure 3 .

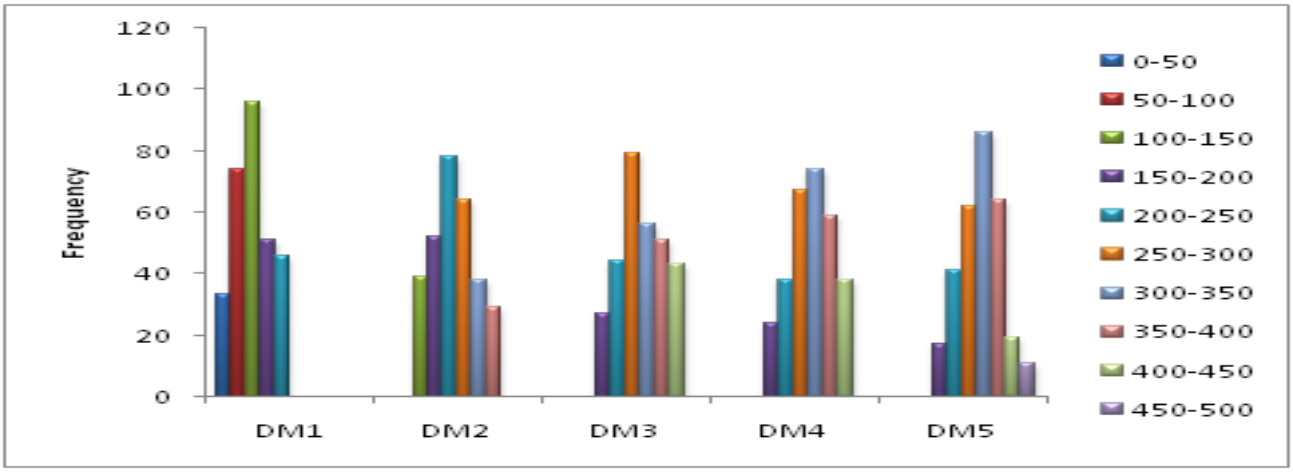
Figure 3: Average diameter of Dapsone microspheres



As the polymer ratio was increased, the average particle size of the microspheres was also found to increase. This increase in

the particle size may be attributed to the increase in the viscosity of the droplets. The number of particles that appeared in a particular size range for the different microsphere formulations was counted and the frequency distribution data was analyzed. The results are represented in figure 4.

Figure 4: Frequency distribution of Dapsone microspheres



Entrapment Efficiency

Table 3: Drug entrapment efficiency of microspheres

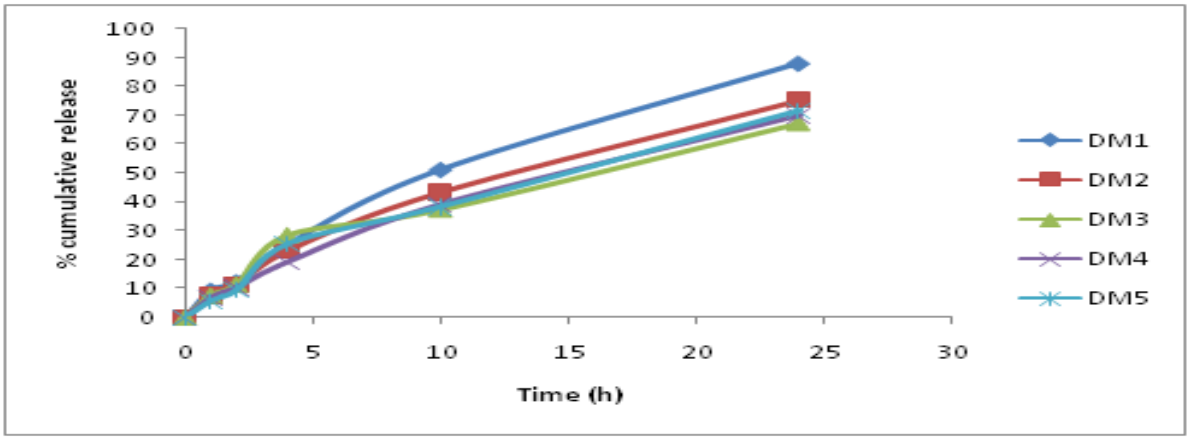
Formulation code	Percent Yield (%)	Surface adsorbed drug (mg)	entrapped drug (mg)	total entrapped drug (%)
DM1	81.6	3.8	28.7	65
DM2	87.1	3.4	29.6	66
DM3	79.8	3.7	31.4	70.2
DM4	88.3	2.8	32.3	70.2
DM5	86.9	2.3	32.9	70.4

The percent drug entrapment in various formulations was determined after extracting the drug with trichloroacetic acid and estimating the content of Dapsone at 295 nm using UV visible spectrophotometry. The result of percent entrapment efficiency and yield are shown in table 3.

In vitro release of Dapsone from microspheres

The in vitro release study of Dapsone from the microspheres exhibited prolonged and controlled release of Dapsone for more than 24 h. The results of the in vitro release studies of the formulations DM1 to DM5 are presented in figure 5.

Figure 5: Comparative % cumulative release of Dapsone from microspheres



A maximum of 88.12 ± 0.79 % Dapsone release was observed in the formulation DM1 after 24 h whereas the steadiest and controlled release was found in DM4 (69.73 ± 0.72%).

Release Kinetics

The regression coefficient of determination of release kinetics (table 4) indicated that the release data was best fitted with first order kinetics while the Higuchi equation explains the diffusion-controlled release mechanism.

The most optimum formulation in terms of controlled release was found to be DM4 and it was incorporated into gel formulation using HPMC as the gelling agent. Physical characteristics and drug content

Table 4: Regression coefficient (r^2) values of different kinetic models

Formulation	Zero order	First order	Higuchi	Peppa's
DM1	0.970	0.993	0.970	0.912
DM2	0.968	0.999	0.979	0.918
DM3	0.935	0.980	0.928	0.929
DM4	0.977	0.999	0.987	0.916
DM5	0.961	0.992	0.959	0.910

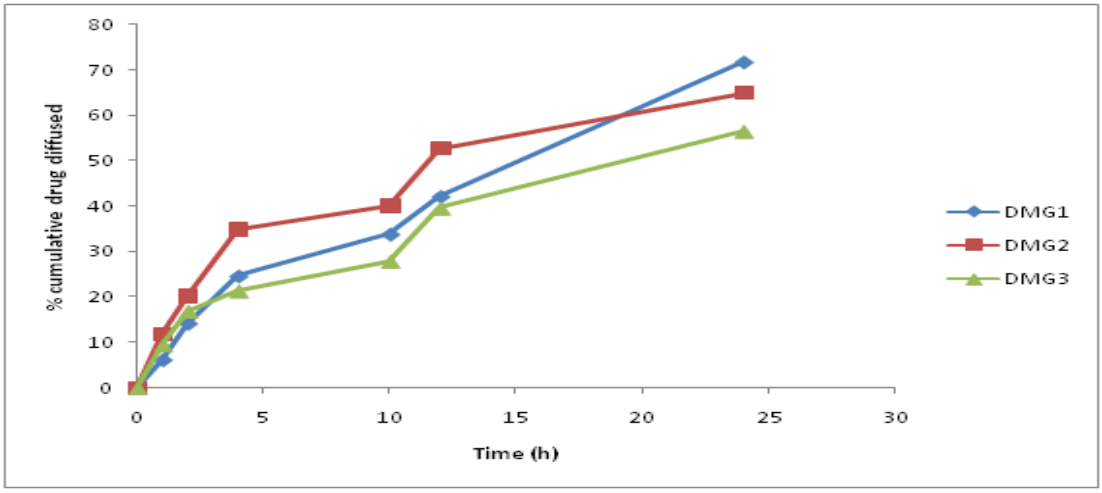
All the three gel formulations were homogenous with no visible grittiness and uniform in consistency. The data of the evaluated gel formulations are represented in table 5; all the

parameters were found to be in acceptable limits.

The consistency of the formulations was found to be proper in all the batches and the viscosity increased in formulations with higher amount of HPMC. In vitro diffusion from gel.

The in vitro diffusion studies were performed using Franz-diffusion cell employing egg membrane as the skin simulation membrane. The diffusion was studied for 24 h and it was found that DMG1 diffused maximum amount (as indicated by drug released in buffer) (figure 6).

Figure 6: Diffusion curve of Dapsone (DM4) from gel formulation



Though the maximum amount of drug released from DMG1 but due to its low viscosity and very high spread ability, it was much likely to be affected by variation in temperature conditions while transport and storage. Hence DMG2, containing 1.0% HPMC, and exhibiting 64.91% drug release after 24 h from the gel formulation was considered as the most optimum formulation.

CONCLUSION

The present study was aimed to control and prolong the release of Dapsone by formulating and microspheres and incorporating in to gel dosage form for topical application with a reduced frequency of application and hence lesser known side effects. The present work was able to demonstrate that chitosan microspheres loaded with the lipophilic drug Dapsone could be effectively prepared using suspension polymerization technique. The easy incorporation of the microspheres into gel formulation and a good amount of drug diffusion after 24 h of study justify the hypothesis.

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Declaration of interest

The authors declare no conflict of interests.

REFERENCES

1. Chein YW, 2005. Concepts and system design for rate-controlled drug delivery. In Swarbrick. J (Editor). Novel Drug Delivery System, New York; Marcel Dekker Inc, pp. 1-39
2. Bruck SD, 1983. Pharmacological basis of controlled drug delivery. In: Bruck, SD (Editor). Controlled Drug Delivery. Volume I, Florida, CRC Press Inc, pages. 1-14
3. Radley K, Tucker R, 2013. Dapsone in the Management of Acne Vulgaris. Journal of the Dermatology Nurses Association. 5(6), pages- 316-319. Doi: 10.1097/JDN.0000000000000008
4. Jakhar S, Kadian V, Rao R, 2021. Dapsone-loaded Microsponge Gel for Acne Management: Preparation, Characterization and Anti-microbial Activity. Micro and Nanosystems. 13(2), pages-211-222. Doi: 10.2174/1876402912999200630130442
5. Acharya N, Shah P, Patel G, et al, 2020. Formulation, development and optimization of Dapsone depot injection in acne: in-vitro/in-vivo study. International Journal of Pharmaceutical Science Research. 11(7), pages- 3417-3426
6. Ranjbar M, Khazaeli P, Pardakhty A, et at, 2019. Preparation of polyacrylamide/polylactic acid co-assembled core/shell nanofibers as designed beads for Dapsone in vitro efficient delivery. Artificial Cells, Nanomedicine and Biotechnology. 47(1), 917-926. Doi: 10.1080/21691401.2019.1577881
7. Tiwari R, Tiwari G, Wal P, et al, 2018. Development, Characterization and Transdermal Delivery of Dapsone and an Antibiotic Entrapped in Ethanolic Liposomal Gel for the Treatment of Lepromatous Leprosy. The Open Nanomedicine and nanotechnology Journal. 5, Pages – 1 - 15. Doi: 10.2174/1875933501805010001
8. El-Nabarawi MA, Shamma RN, Farouk F, et al, 2018. Dapsone-Loaded Invasomes as a Potential Treatment of Acne: Preparation, Characterization, and In Vivo Skin Deposition Assay. American Association of Pharmaceutical Scientist. 19, Pages-2174-2184. DOI: 10.1208/s12249-018-1025-0
9. Deshkar SS, Bhalerao SG, Jadhav MS, et al, 2017. Formulation and Optimization of Topical Solid Lipid Nanoparticles based Gel of Dapsone Using Design of Experiment. Pharmaceutical Nanotechnology. 6(4), Pages – 1 - 11. Doi: 10.2174/2211738506666181105141522
10. Mahore JG, Suryawanshi SD, Shirolkar SV, et al, 2017. Enhancement of Percutaneous Delivery of Dapsone by

Microemulsion Gel. Journal of Young Pharmacists. 9(4), Pages-507-512. Doi: 10.5530/jyp.2017.9.99

11. Farhangi M, Dadshzadeh S, Bolourchian N, 2017. Biodegradable Gelatin Microspheres as Controlled Release Intraarticular Delivery System: The Effect of Formulation Variables. Indian Journal of Pharmaceutical Sciences. 79 (1), Pages - 105-112.
12. De A, Dey S, Pradhan PK, et al, 2014. Estimation of Dapsone in bulk & dosage form by UV spectroscopic method. Indo American Journal of Pharmaceutical Research. 4 (1), Pages-312-319.
13. Semalty M, Yadav S, Semalty A, 2010. Preparation and characterization of gastroretentive floating microspheres of Ofloxacin hydrochloride. International Journal of Pharmaceutical Sciences and Nanotechnology. 3 (1), Pages-819-823. Doi: 10.37285/ijpsn.2010.3.1.4
14. Shaikh KS, Chellampillai B, Pawar AP, 2010. Studies on nonionic surfactant bilayer vesicles of ciclopirox olamine. Drug Development and Industrial Pharmacy. 36(8), Pages – 946 - 953. Doi: https://doi.org/10.3109/03639040903585150
15. Rekha U, Manjula BP, 2011. Formulation and evaluation of microsponges for topical drug delivery of Mometasone furoate. International Journal of Pharmacy Pharmaceutical Sciences. 3(4), Pages-133-137.
16. Pandey T, Kumar A, Sharma R, 2021. Effect of essential oils as penetration enhancers for ibuprofen loaded transdermal gel formulations. Journal of Pharmacology and Biomedical. 5(2), Pages-268-276.
17. Panda P, Ghosh A, 2010. Formulation and Evaluation of Topical Dosage Form of Eupatorium Odoratum Linn and Their Wound Healing Activity. International Journal of Pharma and Bio Sciences. 1(2), Pages- 201-203.
18. Purushothamrao K, Khaliq K, Sagare P, et al, 2010. Formulation and evaluation of vanishing cream for scalp psoriasis. International Journal of Pharmaceutical Science and Technology. 4(1), Pages- 33-41.
19. Pandey T, Kumar A, Sharma R, 2021. Effect of essential oils as penetration enhancers for ibuprofen loaded transdermal gel formulations. Journal of Pharmacology and Biomedical. 5(2), Pages- 268-276.

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