Research Article

PHARMACODYNAMIC ACTIVITY OF CURCUMIN GELS PRODUCED FROM CURCUMIN SOLID LIPID NANOPARTICLES FOR RHEUMATOID ARTHRITIS

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ABSTRACT

The present work is the development and pharmacodynamic assessment of curcumin gels for targeted delivery at joints due to less expected side effects of the herbal component compared to NSAIDs. Initially curcumin was prepared as solid lipid nanoparticles (SLN's) to enhance solubility and dissolution. 10 formulations were prepared by solvent injection method by changing the concentration of stearic acid. They were evaluated by percentage drug content, *in-vitro* release, particle size, zeta potential, DSC and FTIR analysis. Percentage drug content for all formulations was in the range of 98.7 to 99.3%. F7 and F8 formulations has more drug release of 81.32% and 89.17%. Particle size of formulations F7 and F8 were 314.9 nm and 214.9 nm and zeta potential was -30.1 and -26.5 respectively. DSC and FTIR analysis indicated there is no interaction between the drug and polymers. The promising SLN's F7 and F8 were converted into gel using carbopol 934 and sodium carboxy methyl cellulose. Gels were evaluated for homogeneity, physical appearance, viscosity, pH, *ex-vivo* permeation studies and *in-vivo* pharmacodynamic activity. Prepared gels were homogenous, yellowish in color, viscosity ranges from 29000-42000 with a pH of 7.0. *Ex-vivo* permeation studies of gels prepared with 1:3 ratio of carbopol and sodium carboxy methyl cellulose formulation has more drug release of 96.39% than other gels. From *in-vivo* studies it was evident that at the end of the experiment, inflammation on both hind paws of rats treated with curcumin gel were reduced compared to untreated rats.

Keywords: Curcumin, SLN's, Gel, *ex-vivo* permeation studies, pharmacodynamic activity.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, systemic inflammatory disease of unknown etiology that affects 0.5-1.0% of the general population. The incidence of arthritis is more common among women and there are high rates of disease onset associated with pregnancy. Nearly 66% of people with arthritis are younger than 65 years of age. Arthritis affects adults and children of all races and global prevalence is expected to soar in the coming decades. RA has been treated with a combination of anti-inflammatory drugs and immunosuppressant drugs to reduce inflammation and even immune system function. Unfortunately, these approaches can create problems due to side effects that include stomach damage, susceptibility to infections, and increased cancer and cardiovascular risk because all of the drugs in use have severe, potentially life threatening consequences due to non-specific targeting, often in combination with impaired immune function^{1,2,3}.

Curcumin, a natural ingredient indicated to possess immune system modulation, protection from oxidative stress and joint comfort. Studies⁴ revealed that a highly bioavailable form of curcumin was more effective in alleviating RA symptoms, including tenderness and swelling of joints than other drugs. As it is natural compound the curcumin group had another benefit i.e., lack of adverse effects and side effects. Easy availability, low cost. Curcumin, profoundly reduces joint inflammation and destruction, presumably by blocking inflammatory pathways and thereby preventing the increased production of a protein that triggers swelling and pain. It is most known for its potent anti-inflammatory properties and it can inhibit both the excessive

activity and the synthesis of cyclooxygenase-2 (COX2) and 5-lipoxygenase (5-LOX), as well as other enzymes that have been implicated in inflammation. Though curcumin has many beneficial effects, the biggest challenge to curcumin has been absorption. Because of this, larger dosages (up to 10 to 12 g daily) are required to get even a small amount into the bloodstream⁵. While no toxicity is associated with curcumin, even at these very high dosage levels, cost, comfort and compliance can be difficult issues to resolve for many people.

Literature revealed oral formulations of curcumin for treatment of Rheumatoid arthritis(RA). Hence the present research was aimed at development of easily used convenient gel preparations for treatment of RA as targeted drug delivery systems and to assess their effect against treatment of RA. The major steps involve initially the preparation of solid lipid nano particles of curcumin and to conversion of optimised SLN's to gel including *in-vitro* evaluation and *in-vivo* assessment of pharmacodynamic activity using rheumatoid induced rats as animal model.

MATERIALS AND METHODS

Curcumin and Stearic acid was purchased from Molychem, India. Poloxomer 188 and Betamethasone was purchased from Hi media, India. Carbopol and Sodium Carboxy Methyl Cellulose was purchased from SD fine chemicals Ltd. Bovine type II Collagen and Incomplete Freund's Adjuvant was purchased from Chondrex, U.S.A. was purchased from Hi media, India. All the other chemicals and reagents used were of analytical grade.

Preparation of SLN's of Curcumin

10 Formulations of solid lipid nanoparticles of curcumin were prepared by solvent injection method^{6,7,8} and their composition is shown in Table 1. Curcumin and stearic acid were dissolved in ethanol with gentle heating. It was then injected rapidly in to aqueous phase containing poloxomer (2%) which was continuously stirred at 400 rpm for 30 min on a magnetic stirrer (Remi equipments, Mumbai). 0.1N HCl was added to the dispersion then it was centrifuged at 10000 rpm for 30 min using centrifuge (Remi equipments, Mumbai). Aggregates were resuspended in solution of poloxomer (4%) and it is stirred at 1000rpm for 10 min. Then it was filtered under vacuum and dried in lyophilizer (Lyodel freeze dryer).

All the prepared formulations F1 to F10 were evaluated by percentage drug release, *in-vitro* dissolution, Particle size, Zeta potential, DSC, FTIR. SLN's which has highest dissolution (81.32%) (89.17%) i.e., F7 and F8 formulations having the particle size of 214nm and 314nm respectively were converted as gel.

Preparation of gel

12 trial formulations of gels were prepared using carbopol and sodium carboxy methyl cellulose as gelling polymers in various ratios and shown in Table 2. Carbopol 934, Na CMC and water was taken in a beaker and it was soaked for 24 h. SLN's equivalent to contain 500 mg of curcumin was added to gel base with continuous stirring with mechanical stirrer. Then it was neutralised with sufficient quantity of triethanolamine (1-2 drops). 1- 2 drops of glycerine and benzyl alcohol was added to the gel base with slow and continuous stirring^{9,10,11}. In each trial 5 gm of gel was prepared.

Evaluation of Curcumin SLN's Drug content analysis for SLN's

SLN's equivalent to contain 100 mg of curcumin were weighed and dissolved in 5 ml of ethanol and made up the volume to 100 ml with phosphate buffer 5.5. The solution was filtered through filter and drug content were analysed by UV-Visible spectrophotometer (Schimdu, India) at 421 nm¹². Three trials were carried out and the average percent drug content was estimated.

In-vitro drug release studies

The cumulative percent drug release was determined using dissolution testing apparatus (USP II paddle type, Electrolab, India). Dissolution medium was 900 ml of pH 5.5 phosphate buffer maintained at 37 ± 0.5 °C and at agitation of 100 rpm. The study was continued for another 8 hours. A 5 ml sample solution was withdrawn at appropriate time intervals and filtered and the concentration of curcumin at each sampling time was analyzed using UV-Visible spectrophotometer at lamda max of 421nm¹³.

Particle size and zeta potential

Particle size (z-average diameter) and Zeta potential was estimated by Zetasizer, Zeiss ultra(FESEM) for promising formulation F7 and F8 having high drug release values of 81.32% and 89.17% respectively. Before measurement, the nanoparticles dispersion was appropriately diluted to yield a suitable scattering intensity with ultra-pure water. For particle

size the diluted nanoparticles dispersion was poured into the cuvette which was placed in the cuvette holder of the instrument and analyzed using the zetasizer software (Zeiss ultra(FESEM))¹⁴. For zeta potential measurement folded capillary cuvette was used.

Differential Scanning Calorimetry

Thermal behavior of curcumin loaded SLNs was analyzed using differential scanning calorimeter (Mettler toledo, Switzerland). Approximately 10 mg of samples was placed in aluminum crimp cells and subjected to DSC under constant purging nitrogen at 20 ml/min. Thermograms were recorded by heating samples from 30°C to 200°C at a heating rate of 10°C/min with empty aluminium pan as the reference.

Fourier transform infra red spectroscopy

FTIR (Bruker, Japan) study was done for formulation F8 by pressed pellet technique¹⁵. Prepared KBr pellets were scanned between wave number regions of 4000-400 cm⁻¹.

Evaluation of gels Homogeneity

All developed gels were tested for homogeneity by visual inspection after the gels have been set in container. They were tested for their appearance and presence of any aggregates.

Physical evaluation

Physical parameters such as color and appearance was evaluated by physical inspection.

pH measurement

pH of the gel was measured by using pH meter (Remi, INDIA).

Viscosity and Rheological studies

The viscosity of gels was determined by using Brookfield viscometer. The gel was placed in the sample holder and the suitable spindle selected was lowered perpendicularly into the sample. The spindle was attached to viscometer and then it was allowed to rotate at a constant optimum speed at room temperature. The readings were noted after 2 minutes.

Ex-vivo permeation studies

Ex-vivo permeation studies were conducted using goat skin. Hair on the goat skin was shaved using a hand razor and adhering subcutaneous fat was carefully cleaned. A system having modified Franz's diffusion cells with a diffusional area of 2.15 cm was used for permeation studies. Pretreated goat skin was set in place with the stratum corneum facing the donor compartment and the dermis facing the receptor compartment in the Franz diffusion. The receptor compartment was filled with 25 ml of phosphate buffer 7.4. 0.5 gm of gel was applied to the skin membrane over an area of 1.131 cm² and placed across the donor compartment. The temperature of the diffusion medium was maintained at 37 ± 2 °C and stirred at 100 rpm. Samples (1 ml) was withdrawn for 0, 15, 30, 45, 60, 90 and 120 min and replaced with an equal volume of fresh buffer to maintain sink conditions¹⁶. Samples were analysed spectrophotometrically at 421 nm.

Pharmacodynamic studies**Induction of arthritis**

Male albino wistar rats were injected subcutaneously with 200 µg of bovine type II collagen emulsified with incomplete Freund's adjuvant at the base of the tail until needle tip reaches 0.5 cm from the base. Needle length should be completely subcutaneous and wiped before each injection to prevent leakage of emulsion. Onset of arthritis in rats is much faster than mice (around 4 weeks) and clinically apparent arthritis with swollen joints appears around 12-14 days after the immunization¹⁷.

Gel exhibiting highest diffusion was studied for antiarthritic effect by using male albino wistar rats as animal model. (Ethical committee Reg.no:1677/PO/A/12/1AEC, May 2016) Rats were divided in to five groups. Each group contains 6 rats.

Group I: Normal (will receive vehicle used to reconstitute the drug)

Group II: Disease control (arthritis induction but no drug given)

Group III: Arthritis induction then given standard drug (Betamethasone 0.5 mg/ml/kg)

Group IV: Arthritis induction then given SLN's of Curcumin orally (110 mg/ml/kg)

Group V: Arthritis induction then given Curcumin gel topically.

Treatment

After 14 days of induction, group I and group II rats are given with vehicle (olive oil). Group III rats are treated with betamethasone orally which is suspended in olive oil. Group IV rats are treated with SLN's of curcumin orally which is also suspended in olive oil¹⁸. Group V are treated with curcumin gel which is applied topically.

Arthritis score assessment

After induction of arthritis with bovine type II collagen, occurrence and extremity of arthritis in rats were observed for every 2 days. Swelling and inflammation of both hind paws were graded from 0 to 4 according to Brand et al. (2007) which was given in the Table 3. Arthritis score for each rat were calculated by observing both hind paws¹⁷

Radiology score assessment

On the last day of treatment i.e., 42nd day rats were anaesthetised with 0.1 ml of Ketamine and 0.15 ml of xylazine per 100 g of body weight of rat. Then the rats which are normal and arthritis induced were kept on radiographic machine to capture X-ray photograph¹⁷.

Table 1: Composition of SLN's of curcumin

S.No	1	2	3	4	5	6	7	8	9	10
Formulation code	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Drug (mg)	500	500	500	500	500	500	500	500	500	500
Stearic acid(mg)	50	100	150	200	250	300	500	750	800	900

Table 2: Composition of gels containing SLN's of curcumin

S.no	1	2	3	4	5	6	7	8	9	10	11	12
Carbopol: Na CMC	1:1			1:2			1:3			2:1		
Form of drug	PC	F7	F8	PC	F7	F8	PC	F7	F8	PC	F7	F8

Note: PC= Pure curcumin

Table 3: Qualitative scoring system used to assess severity of paw inflammation

Score	Condition
0	Normal
1	Mild, but definite redness and swelling of the ankle or wrist, or apparent redness and swelling limited to individual digits, regardless of the number of affected digits
2	Moderate redness and swelling of ankle or wrist
3	Severe redness and swelling of the entire paw including digits
4	Maximally inflamed limb with involvement of multiple joints

Table 4: Interpretation of FTIR spectra of curcumin and SLN's of curcumin

Functional groups	Wave number of curcumin (nm)	Wave number of SLN's of curcumin (nm)
O-H	3612.06	3610.79
Ar.C-H	2971.86	2917.32
Alk C-H	2848.96	2848.86
C=O	1629.30	1602.22
C-O	1204.70	1205.76

Table 5: Viscosity of prepared gels

S.no	1	2	3	4
Carbopol: Na CMC	1:1	1:2	1:3	2:1
Viscosity (Cp)	34000	38000	42000	29000

Table 6: Arthritis score analysis

Day	Arthritis score (mean $\pm$ S.D)				
	Group I	Group II	Group III	Group IV	Group V
0	0.00 $\pm$ 0.00	0.00 $\pm$ 0.00	0.00 $\pm$ 0.00	0.00 $\pm$ 0.00	0.00 $\pm$ 0.00
14	0.00 $\pm$ 0.00	1.50 $\pm$ 0.02	1.33 $\pm$ 0.01	1.51 $\pm$ 0.02	1.66 $\pm$ 0.03
18	0.00 $\pm$ 0.00	2.13 $\pm$ 0.01	1.39 $\pm$ 0.01	2.09 $\pm$ 0.03	1.53 $\pm$ 0.02
22	0.00 $\pm$ 0.00	2.65 $\pm$ 0.05	1.24 $\pm$ 0.03	2.16 $\pm$ 0.02	1.34 $\pm$ 0.04
26	0.00 $\pm$ 0.00	2.95 $\pm$ 0.03	1.19 $\pm$ 0.02	2.11 $\pm$ 0.06	1.26 $\pm$ 0.03
32	0.00 $\pm$ 0.00	3.26 $\pm$ 0.02	1.08 $\pm$ 0.05	2.05 $\pm$ 0.03	1.11 $\pm$ 0.02
34	0.00 $\pm$ 0.00	3.59 $\pm$ 0.05	1.04 $\pm$ 0.02	2.04 $\pm$ 0.05	1.05 $\pm$ 0.03
38	0.00 $\pm$ 0.00	3.84 $\pm$ 0.04	0.85 $\pm$ 0.06	2.04 $\pm$ 0.02	0.99 $\pm$ 0.04
42	0.00 $\pm$ 0.00	3.98 $\pm$ 0.06	0.77 $\pm$ 0.05	2.02 $\pm$ 0.06	0.81 $\pm$ 0.05

*n=6

Table 7: Photograph and X-ray images of both hind paws of rat

S.N	Group treated as / with	Photograph of rat		X-ray of rat	
		Right paw	Left paw	Right paw	Left paw
1.	Control
2.	Disease control
3.	Standard
4.	SLN's of Curcumin oral
5.	Curcumin gel

Figure 1: In-vitro drug release profile of pure curcumin, F1, F2, F3 and F4 formulations

Figure 2: In-vitro drug release profile of F5, F6, F7, F8, F9 and F10 formulations

Figure 3: Zeta size of F7 formulation

Figure 4: Zeta size of F8 formulation

Figure 5: Zeta potential of F7 formulation

Figure 6: Zeta potential of F8 formulation

Figure 7: DSC of pure curcumin

Figure 8: DSC of SLN's of curcumin

Figure 9: FTIR spectra of pure curcumin

Figure 10: FTIR spectra of SLN's of curcumin

Figure 11: 1:1 ratio carbopol and NaCMC gels

Figure 12: 1:2 ratio carbopol and NaCMC gels

Figure 13: 1:3 ratio carbopol and NaCMC gels

Figure 14: 2:1 ratio carbopol and NaCMC gels

RESULTS AND DISCUSSION

All the prepared SLN's shows the drug content in the range of 98 – 99 % indicating negligible loss during the preparation. Dissolution profile was represented in Figure 1 and 2. The results of dissolution studies evidenced that all the prepared formulations have drug release more than pure curcumin. Among all formulations F7 and F8 evidenced high drug release of 81.32% and 89.17% respectively.

Particle size of F7 and F8 formulation was found to be 314.9 nm and 214.9 nm respectively and represented in Figure 3 and 4. which indicates that the solid lipid nanoparticles prepared were in nano size and the zeta potential was found to be -30.1 and -26.5 which shows that the prepared SLN's were stable, represented in Figure 5 and 6. DSC of pure curcumin and SLN's of curcumin was found to be 180°C and 173°C respectively and represented in Figure 7 and 8, shows that there is no interaction between drug and excipients.

Both FTIR of pure curcumin and SLN's of curcumin represented in Figure 9 and 10. IR absorption of major functional groups of curcumin and its SLN's is shown in Table 4, there is a slight shift of peaks indicating there is no interaction of polymer with the curcumin.

Characterization for gels

All the prepared gels were homogenous, yellowish in color with pH of 7.0. indicating no skin irritation. Drug content values in the range of 98.7% – 99.3 % indicated negligible loss of drug during preparation. The viscosity values were represented in Table 5 indicated that the viscosity of the gels was increased upon increase of sodium CMC concentration.

Ex-vivo permeation studies

The results of *ex-vivo* permeation studies are represented in Figure 11,12,13 and 14. Of all the 12 formulations of gels, the gel made with F8 formulation and carbopol and Na CMC in 1:3 ratio showed high cumulative drug release (76.93%) in half an hour of application on skin membrane. Its highest cumulative drug release was 96.39% in 120 minutes.

In-vivo pharmacodynamic activity Arthritis score assessment

Swelling and inflammation was observed from 14th of immunisation. Each group contain 6 rats. Arthritis score was measured as mean. From the Table 6 it is evident that the rats which were untreated shows deformities at the end of study. While the rats which were treated with betamethasone and

curcumin gel shows no deformities and swelling of both paws are not significant.

Radiographic analysis

From Table 7 it was observed that both hind paws of rat were swollen and inflamed after 14th day of induction. Treatment was given from fourteenth day to forty two days after induction. At the end of the treatment the inflammation on both hind paws of treated rats were reduced compared to untreated rats. X-ray studies shows that deformities were occur to untreated rats but not to treated rats and inflammation and swelling of paws was reduced in rats treated with standard drug (Betamethasone) and curcumin gel. In rats treated with SLN's of curcumin orally, swelling is not reduced but deformities do not occur as in case of untreated rats.

CONCLUSION

Curcumin gels prepared with carbopol and sodium CMC in the ratio of 1:3 and solid lipid nanoparticles of curcumin produced from stearic acid (750 mg), poloxomer (600 mg) and curcumin (500 mg) was used successfully in the treatment of collagen induced rheumatoid arthritis in rats

REFERENCES

- Charles J. Malemud, Immunotherapies and Rheumatoid Arthritis-Introduction, Clinical & Cellular Immunology, 2013, 1-3
- Gupta Manish, Sharma Vimukta, Targeted drug delivery system: A Review, Research Journal of Chemical Sciences, May (2011), Vol. 1(2), 135-138.
- Lain B. McInnes and Georg Schett, Mechanisms of Disease the Pathogenesis of Rheumatoid Arthritis, review article, The new england journal of medicine; 2011, 2205-2219.
- Amandeep Kaur, Herbal Plants used in treatment of Rheumatoid Arthritis: A Review, International Journal of Pharmacy And Pharmaceutical Sciences, 2012, Vol 4, Suppl 4
- Kapil Kumar, A.K. Rai, Curcumin: A yellow magical spice of kitchen for treatment of rheumatoid arthritis, International Research Journal of Pharmacy, 2011, 2(12), 29-31.
- J. Chen, W. T. Dai, Fabrication and Evaluation of Curcumin-loaded Nanoparticles based on Solid Lipid as a New Type of Colloidal Drug Delivery System, Indian Journal of Pharmaceutical Science, 2013 Mar-Apr; 75(2): 178-184.
- Fathy I. Abd-Allah, Hamdy M, Application of solvent injection method to develop stable, sustained release solid lipid nanoparticles of curcumin, International Journal of

- Development Research, Vol. 4, Issue, 12, Pp. 2734-2742, December, 2014.
8. Sarathchandiran, A review on nanotechnology in solid lipid nanoparticles, *International journal of pharmaceutical development and technology*, ISSN- 2248-910X, (1), 2012, 45-61.
 9. Sujit Kumar Debnath, Sibaji Sarkar, Formulation and Evaluation of Aceclofenac Gel, *International Journal of ChemTech Research*, April-June 2009, Vol.1, No.2, pp 204-207.
 10. Sanju Dhawan, Bikash Medhi, Formulation and evaluation of diltiazem hydrochloride gels for the treatment of anal fissures, *Scientia Pharmaceutica*, 2009; 77: 465-482.
 11. Aijaz .A. Sheikh , Siddique.S.Ali, Formulation development and characterization of aceclofenac gel containing linseed oil and ginger oleoresin, *International Journal of PharmTech Research*
 12. Narahari N Palei, Malay K Das, Preparation and characterization of lornoxicam loaded solid lipid nanoparticles made from different lipids, *International Journal of Pharmacy and Pharmaceutical Sciences*, ISSN- 0975-1491 Vol 5, Suppl 4, 2013.
 13. Poonam Yadav, Girish Soni, Development and characterization of solid lipid nanoparticles by solvent diffusion- evaporation method for topical delivery, *International Journal of Pharmaceutical Sciences and Research*, ISSN: 2320-5148, 2014; Vol. 5(3): 1028-1034.
 14. J. Chen, W. T. Dai, Fabrication and Evaluation of Curcumin-loaded Nanoparticles based on Solid Lipid as a New Type of Colloidal Drug Delivery System, *Indian Journal of Pharmaceutical Science*, 2013 Mar-Apr; 75(2): 178-184.
 15. Maheshkumar P. Soni, Nilakash Shelkar, Buparvaquone loaded solid lipid nanoparticles for targeted delivery in theileriosis, *Journal of Pharmacy and Bioallied Sciences* January-March 2014 Vol 6 Issue 1.
 16. Preeti, Murugesan Senthil Kumar, Development of Celecoxib Transfersomal gel for the Treatment of Rheumatoid Arthritis, *Indian Journal of Pharmacy and Biological Research*. 2014; 2(2):7-13, ISSN: 2320-9267.
 17. Chondrex, in, Protocol for the Successful Induction of Collagen-Induced Arthritis (CIA) in Rats
 18. A.F. Zahidah, Curcumin as an Anti-Arthritic Agent in Collagen-Induced Arthritic *Sprague-Dawley* Rats, *Sains Malaysiana* 2012), 41(5), 591-595.
 19. Ananta Choudhury, Reema Verma, Development and Characterization of Topical Phyto-Formulation for Antifungal Activity, *Journal of Applied Pharmaceutical Research*, April – June 2014 Volume (XI) Issue 2, ISSN No. 2348 – 0335.
 20. Mallesh Kurakula, C. Srinivas, Formulation and Evaluation of Prednisolone Proliposomal Gel for Effective Topical Pharmacotherapy, *International Journal of Pharmaceutical Sciences and Drug Research* 2012; 4(1): 35-43, ISSN 0975-248X.
 21. Ananta Choudhury, Reema Verma, Development and characterization of topical phyto-formulation for antifungal activity, *Journal of Applied Pharmaceutical Research*, April – June 2014 Volume (XI), issue 2, ISSN No. 2348 – 0335.

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