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Development and Evaluation of Transdermal Patch of Curcumin for Rheumatoid Arthritis

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Abstract

Conventional drug delivery system has many problems so bulk of research has now shifted from synthetic drugs to herbal drugs. This is possible because of the vast variety of bioactive molecules in the plants and their higher safety margin. This present study is focused on the use of curcumin, the active constituent of *Curcuma longa* (haldi), belonging to family *Zingiberaceae* as an antiinflammatory agent against rheumatoid arthritis. The main objective of present work was to develop the transdermal patch of curcumin using different polymer blends so that minimize the side effects and maximize the therapeutic efficacy. The formulations were also evaluated for weight variation, drug content, thickness, moisture content, folding endurance, *in vitro* drug release, flux, stability studies etc., shows satisfactory results

Keywords*:*

Curcumin, Formulation, Rheumatoid arthritis, Transdermal patch

Introduction

Among many inflammatory diseases rheumatoid arthritis (RA) is a major disease which is caused due uric acid crystal formation in the joints which causes inflammation**.** Rheumatic diseases have affected mankind since ages and are one of the commonest inflammatory conditions in developing countries. Rheumatoid arthritis forms a major prototype of rheumatic diseases and is a common cause of disability. RA is both an extravascular immune complex disease and a disorder of cell mediated immunity leads to chronic inflammation, granuloma formation and joint destruction. The etiopathogenesis of RA involves diverse and complex factors such as genetic background, rheumatic factor (circulating antibodies), immune complexes, compliment activation, lymphocytes, arachidonic acid metabolites, free oxygen radicals etc. Currently synthetic drugs form a major line of treatment in the management of arthritis. The conventional drug treatment of RA consists of analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), disease modifying anti rheumatic drugs (DMARDs) and corticosteroids.

Transdermal Patch: Transdermal patch is a device for delivering the therapeutic substances through the skin for systemic effect at predetermined and controlled rate; comprising of backing membrane, drug incorporated into matrix, release liner and with/without rate controlling membrane.

Curcumin: Curcumin the active constituent of *Curcuma longa* has reported antiinflammatory activity. Curcumin has low absorption from GIT as it is rapidly metabolized. Reasons for use of curcumin are its therapeutic efficacy, easy availability, low cost, less reported side effects.

Experimental

Materials

Curcumin was purchased from Kuber Implex Pvt. Ltd., Indore, India. PVP (CDH New Delhi, India), PVA (CDH New Delhi, India), and all other chemicals were analytical grade from my institute

Solubility

Qualitative Solubility: Qualitative solubility analysis for curcumin was done by dissolving 5 mg of drug in 5 ml of solvent. Different solvents were used for the solubility determination in different solvents like distilled water, 7.2 pH saline phosphate buffer, 7.4 pH saline phosphate buffer, ethanol, methanol, acetone, chloroform, to determine the solubility of drug.

Quantitative Solubility: Quantitative solubility analysis for curcumin was done by taking 5 ml of each solvent and adding the drug gradually into the solvent till saturation was attained. This is to determine the capacity of the solvent

for dissolving drug in each solvent. Different solvents were used for the solubility determination like distilled water, 7.4 pH saline phosphate buffer, 7.2 pH phosphate buffer, methanol, ethanol, mixture of buffer and ethanol. The concentration of drug was measured by UV spectrophotmetric technique.

Identification of Drug

The identification of drug was done by UV spectrophotometric method. Small amount of drug was dissolved in methanol and the solution was scanned in UV visible Spectrophotometer between 200-600 nm.

From the spectra, λmax of curcumin was observed at 422 nm. The spectral data from this scan was used for the preparation of calibration curve of curcumin.

Melting Point

Melting point determination of curcumin was done by using melting point apparatus. In this method the pre sealed capillary was filled with small amount of drug. Capillary and thermometer was placed in melting point apparatus. The temperature was noted when the drug started to melt till the drug completely melted.

Partition Coefficient

Partition coefficient determination of curcumin was done by simple shaking flask method. 10 mg of drug was dissolved in 10 ml of distilled water and 10 ml of carbon tetrachloride in separating funnel. It was shaken well for 24 h by orbit shaker then allowed to stand for complete phase separation. Both the phase were separated out. The sample from carbon tetracholride was diluted accordingly to measure the concenteration of drug. The concentration of drug was measured by UV spectrophotometric method. The remaining concentration of sample in water phase was calculated by deduction of total amount of drug.

Po/w = Coil/Cwater

Particle Size

Particle size determination of curcumin was done by optical microscopy using stage micrometer. A very little amount of drug was placed on slide 1 drop of liquid paraffin was added on the slide and was observed under microscope. The particle size of about 100 particles was observed under microscope. The average particle size of the drug was calculated.

Least Count = Stage /Ocular

Thin Layer Chromatography

TLC plates were prepared by coating slurry of silica gel G on glass plates. They were dried and activated in hot air oven (115-120 °C). The plates were placed in pre saturated TLC chamber with the solvent system of chloroform:ethanol:glacial acetic acid in the ratio of (94:5:1). Sample was loaded on the plates with the help of capillary. The spots were observed in sunlight. The results were

compared with standard and Rf values of drug.

Drug-Excipient Compatibility Studies

(A) A small amount of drug substance with excipients that is, physical mixture of the drug and excipients (in 1:1 ratio were prepared to have maximum likelihood interaction between them) was placed in a vial and rubber stopper was placed on the vial and sealed properly. A storage period of 2 weeks at 60 °C and the same sample was retained for 2 months at 40 °C. After storage the sample were observed physically for liquefaction, caking, odour or gas formation, discolouration.

(B) The drug-excipient interaction study was performed using silica gel-coated TLC (Thin Layer Chromatography) plates and a mixture of chloroform:ethanol:glacial acetic acid in the ratio of (94:5:1). The TLC plates were prepared using a slurry of silica G. The prepared plates were activated at 110 °C for 15 min. On the activated plates, spots of each solution in methanol containing (a) Curcumin and (b) Curcumin containing different experimental ratio of excipients were applied. The plates were dried in sunlight. The Rf values were calculated from the chromatogram obtained and compared with the Rf values of curcumin alone.

Preparation of Standard Curve

Standard stock solution of curcumin was prepared by dissolving 100 mg drug in 100 ml methanol (1000µg/ml). From this solution 1 ml was taken and diluted upto 10 ml. Again 1 ml was taken from this solution and diluted it upto 10 ml. Aliquot of desired concentration were prepared from this solution by suitable dilutions with methanol. The linearity was observed in the concentration range of 0.5-3.5 µg/ml for curcumin. The absorptivity coefficient of drug at desired wavelengths was determined.

Preparation of Transdermal Patch

Matrix-type transdermal patches containing curcumin were prepared using the different ratios of PVP and EC by solvent evaporation technique in petridish. The two polymers were weighed in requisite ratio as mentioned and were dissolved in chloroform. Di-n-butylphthalate (30% w/w) was used as a plasticizer. In all formulation 20 mg drug was added, into the homogeneous dispersion, by slow stirring with a magnetic stirrer. The uniform dispersion was casted on the backing membrane and allowed to dry at 40 °C for 6 h. The backing membrane was prepared by pouring 4% w/v poly vinyl alcohol (PVA cold) solution followed by drying at 60 °C for 6 hours. They were kept in desiccators until used (Table 1).

Table 1. Ratios of components of different formulations

Code	(mg) EC : Oleic acid (%)	(ml)
F-1	1:5	10
F-2	1:2	10
F-3	2:1	10
F-4	5:1	10

Results and Discussion

Solubility

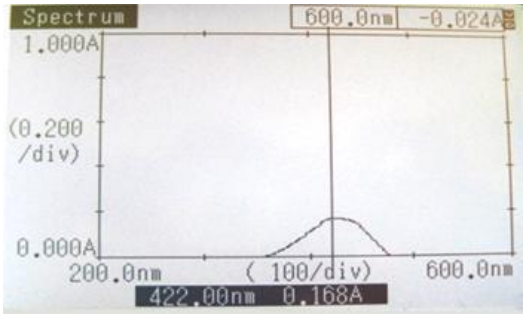
Qualitative solubility studies of drug depicted that the drug is hydrophobic in nature and it is more soluble in organic solvents as compared to hydrophilic solvents. So it can be concluded that drug is lipophillic in nature. Quantitative Solubility: The results of quantitative solubility of curcumin are given below:

- ✓ Distilled water: 0.6 mg of drug was present in 5 ml of distilled water
- ✓ 7.2 pH buffer + ethanol: 9.53 mg of drug was present in 3 ml buffer + 2 ml ethanol
- ✓ Methanol: 12.32 mg of drug was present in 5 ml of methanol
- ✓ Ethanol: 13.45 mg of drug was present in 5 ml ethanol
- ✓ 7.4 pH buffer: 0.94 mg of drug was present in 5 ml of 7.4 pH Buffer.

Quantitative Solubility studies confirm that the drug is lipophillic in nature.

Identification of Drug

The UV scan of the drug sample showed highest peak at 422 nm which is nearby to the standard value. This shows that the drug is pure (Figure 1).



Melting Point

Melting point of drug was found to be 177°C which shows that drug is crystalline in nature because it has sharp melting point. Melting point of drug was found nearby to standard value of melting point of curcumin. So it shows that the drug is pure

Calibration Curve

For preparation of standard curve, solutions of the drug samples were prepared in methanol and there absorbance were measured at 422 nm. The linearity ranges were found to be 0.5-3.5 µg/ml (Figure 2).

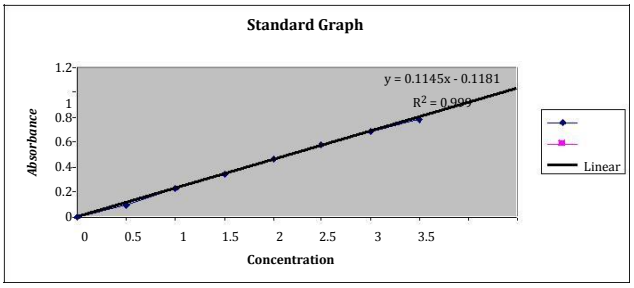


Figure 2. Calibration curve of curcumin at 422 nm in UV.

Partition Coefficient

Partition coefficient of curcumin was found to be 3.66. Partition coefficient of a drug greater than 1 shows lipophillic nature. Results show that the drug is lipophillic in nature. So we can say that the drug curcumin is suitable for transdermal drug delivery system.

Chromatography

The least count was found out to be 1.5 (Table 2). **Table 2.** Particle size distribution of curcumin.

Size range	Mid Point (M.P.)	No. of Particles (n)	M.P. × No. of Particles × L.C. (1.5)=d
0-1	0.5	11	8.25
1-2	1.5	32	72
2-3	2.5	24	90
3-4	3.5	20	105
4-5	4.5	11	74.25
5-6	5.5	2	16.5
		Σn=100	**Σd=366.00**

Particle size distribution shows that the average particle size of drug is 3.66 µm.

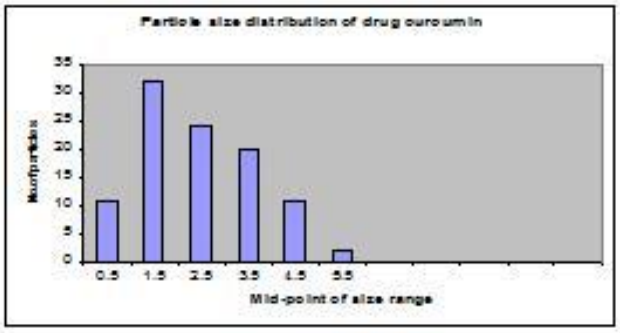


Figure 3. Particle size distribution of curcumin.

Rf value of curcumin

Rf value of curcumin was found 0.86 which was nearby to standard value. So it can be concluded that the drug is pure.

Figure 4. TLC of curcumin

Drug - Excipient Compatibility Studies

After storage the samples were observed physically no change was found. So that can be concluded that there is no interaction between drug and polymers (Table 3).

The Average Rf value of physical mixtures are nearby to the Rf value of drug alone so it can be say that there is no interaction between polymer and drug (Table 4).

Table 3. Drug-excipient compatibility observation.

Additives (50 mg each) with drug	Observation at 60 ^{0}C for 2 weeks	Observation at 40 ^{0}C for 2 months	Remarks
Drug (Curcumin)	No change	No change	Accepted
Drug + PVP	No change	No change	Accepted
Drug + EC	No change	No change	Accepted
Drug + PVP	No change	No change	Accepted
Drug + DBP	No change	No change	Accepted
Drug + Oleic acid	No change	No change	Accepted
Drug + Chloroform	No change	No change	Accepted

Table 4. Thin layer chromatography observation.

Physical Mixtures	Rf Values			Average
	I	II	III	
Drug: Ethyl cellulose	0.76	0.79	0.83	0.79
Drug: PVP	0.81	0.84	0.78	0.81
Drug: PVA	0.85	0.84	0.77	0.83

Evaluation of Formulations

Weight Variation: Weight variation was determined by weighing five films and the average value was taken as the weight of the film. All the formulations exhibited uniform weight with standard deviation values indicating the uniformity of the films prepared by solvent casting method (Table 5).

Thickness: The polymeric combinations showed good film-forming properties and the method of casting on mercury substrate was found to give good films. Low differences between thickness values were found in the thickness of films, which ensured uniformity of thickness of each film (Table 5).

Table 5. Thickness and weight variation observation.

Formulations	Thickness (mm)			Average Thickness Uniformity (mm)	Weight in mg (SD)
	I	II	III		
F-1	0.38	0.41	0.41	0.40	1.33(.06)
F-2	0.48	0.46	0.42	0.42	1.42(.04)
F-3	0.45	0.48	0.49	0.47	1.39(.02)
F-4	0.48	0.44	0.46	0.46	1.37(.06)

Folding Endurance: Folding endurance test results indicated that the films would not break and would maintain their integrity with general skin folding when applied (Table 6).

Drug Content: Good uniformity of drug content among the batches was observed with all formulations. The results indicated that the process employed to prepare films in this study was capable of producing films with uniform drug content and minimal film variability (Table 7.)

Table 6. Folding endurance observation.

Formulation	Folding Endurance			Average
	I	II	III	
F-1	22	24	25	23.6
F-2	16	28	24	22.0
F-3	30	24	26	26.6
F-4	18	34	42	31.3

Table 7. Drug content observation.

Formulation	Drug Content (%)			Average
	I	II	III	
F-1	88.25	87.37	87.81	87.47
F-2	85.00	82.57	86.06	84.54
F-3	92.18	93.49	93.05	92.90
F-4	95.5	96.4	95.5	95.80

Moisture Content*:* Moisture content studies indicated that the increase in the concentration of hydrophilic polymer was directly proportional to the increase in moisture content and of the films, whereas increase in the concentration of hydrophobic polymer lead to the decrease in moisture content of the films. The moisture content of the prepared formulations was low, which could help the formulations remain stable and reduce brittleness during long-term storage (Table 8).

Table 8. Moisture content observation.

Formulation	Moisture Content (%)			Average
	I	II	III	
F-1	2.1	2.0	2.6	2.25
F-2	2.8	3.5	3.5	3.03
F-3	4.4	4.0	4.3	4.25
F-4	5.7	5.2	5.9	5.7

***In vitro permeation studies**:* The *in vitro* skin permeation experiments indicated that release of drug from hydrophilic polymer was more as compared to hydrophobic polymer. Initial rapid dissolution of the hydrophilic polymers occurs when the film is in contact with the hydrated skin, resulting in the accumulation of high amounts of drug on the skin surface and thus leading to the saturation of the skin with drug molecules. The cumulative percent amount of drug released from formulation F-4 (73.7) was high compared to other formulations prepared. The order of release was F-4> F-3>F-2>F-1. The *in vitro* release profiles were subjected to Zero-order, First- order and Higuchi model shows the formulation F-3 exhibited first order kinetics. Formulation F-4 best fit with Higuchi equation (Table 9-10) (Figure 5-8).

Table 9. *In vitro* permeation studies observation data.

Time	Formulations			
(h)	F-1	F-2	F-3	F-4
0	0	0	0	0
1	3.12%	3.1%	3.5%	4.05%
2	3.8%	4.61%	6.62%	8.55%
3	6.7%	8.49%	11.2%	15.17%
4	11.1%	14.32%	18.84%	21.59%
5	17.70%	18.21%	21.5%	27.31%
6	20.5%	20.34%	23.35%	35.39%
7	21.5%	21.89%	25.69%	38.92%
8	22.37%	23.12%	28.21%	40.13%
9	23.87%	24.53%	31.23%	42.43%
10	24.12%	25.97%	34.32%	45.21%
11	26.11%	26.96%	37.14%	46.92%
12	27.32%	28.22%	38.67%	49.73%
24	46.59%	46.98%	65.25%	73.7%

Table 10. R^2 values for different models.

Formulations	R^2 Values		
	Higuchi model	First order	Zero order
F-1	0.945	0.969	0.931
F-2	0.961	0.971	0.966
F-3	0.955	0.995	0.898
F-4	0.964	0.986	0.929

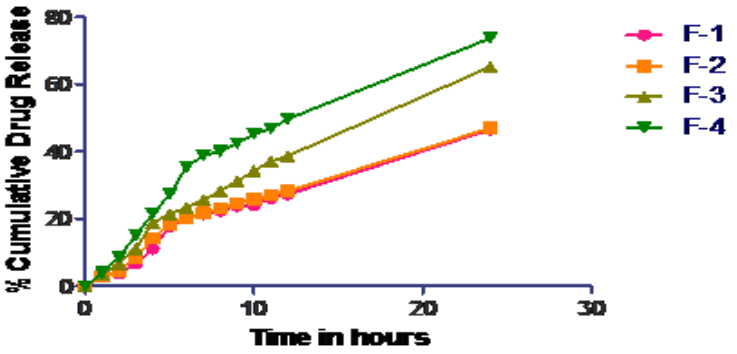


Figure 5. Percent cumulative drug release *vs* time.

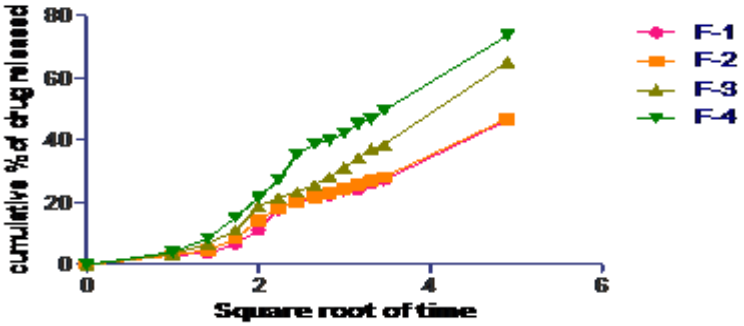


Figure 6 Higuchi graph between cumulative% of drug released *vs* square root of time.

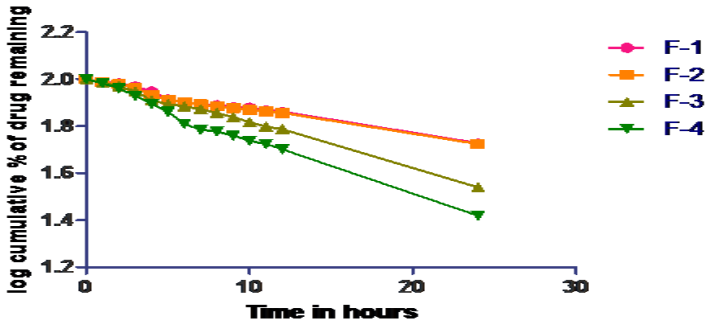


Figure 7. First order graph between log cumulative percent of drug remaining *vs* time.

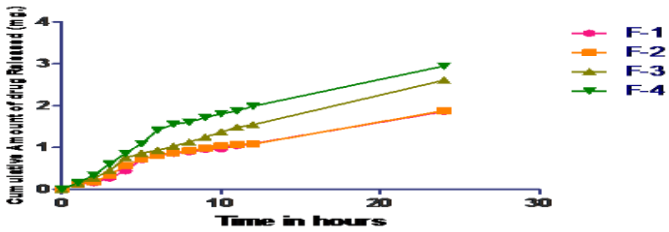


Figure 8. Zero order graph between cumulative amount of drug released *vs* time.

Formulation F-4 shows the good flux through unit cross-sectional area as the amount of hydrophilic polymer increases the flux of formulation was increased (Table 11).

The purpose of stability testing is to determine the quality of the drug substance or drug product varies with time under the influence of environmental factors such as humidity, temperature, light [ICH Q1A (R2)]. To assess the drug and formulation stability, stability studies were done according to ICH guidelines. Optimized transdermal system of different formulation, F-1, F-2, F-3 and F-4, sealed in aluminum packaging coated inside with polyethylene, various replicates were kept in the humidity chamber maintained at 40 °C and 75% RH for 3 months. At the end of studies, samples were analyzed for the drug content. Results are shown below (Table 12).

Table 11. Flux studies observation.

Sr. No.	Formulations	Flux mg/cm^2
1	F-1	0.314
2	F-2	0.329
3	F-3	0.515
4	F-4	0.586

Discussion

In the transdermal drug delivery system the preformulation study for the drug was conducted. The λmax of curcumin was found at 422 nm, which is comparatively same as given in the standards. This shows that the drug is pure. Qualitative solubility studies were showed that the curcumin is insoluble in water, which are same as standards. Results of quantitative solubility was showed that curcumin is more soluble in alcoholic medium as compare to aqueous medium. The partition coefficient was found to be 3.66 the obtained value of partition coefficient of curcumin was more than 1 which showed that the drug is lipophilic in nature which is favorable for TDDS. The average particle size of curcumin was measured by microscopy method was found to be 3.66 µm. The melting point was observed at 177 ^{0}C and it shows the drug is crystaliine in nature. The standard curve of curcumin was prepared in methanol and the r^2 values was obtained 0.999, which shows linearity of absorbance between the range of 0.5-5 ug/ml. TLC plates were developed. Rf

value of curcumin is same which conform that there is no interactions with the excipients. TDDS of curcumin were prepared by using polymers, and evaluated for different parameters. The formulations were also evaluated for weight variation, drug content, thickness, moisture content, folding endurance, *in vitro* drug release, flux, stability studies, etc. shows satisfactory results. All formulations were evaluated for *In vitro* release study. Study was carried for 24 h for all formulation and results show that, the Formulation F-4 shows good cumulative % Release profile of Curcumin. The release data was subjected to different kinetic models shows that the release pattern of F-4 is diffusion mediated; it also shows maximum flux as compare to all other formulation. Stability study was carried out for selected formulation indicated that the formulations are stable enough at different temperature conditions .This study was carried out for three months and this study showed that formulation F-4 was stable during stability testing. The prepared TDDS system were translucent, light yellow to dark orange and smooth in texture, uniform in appearance and show no visible crack or imperfection.

Conclusions

Through the present experimentation, it has found that the drugs of ayurvedic origin can be utilized in a better form with enhanced efficacy by incorporating in modern dosage forms with higher safety margins and minimal side effect. This experimentation is one of the first few attempts to utilize ayurvedic drugs through TDDS. Curcumin the active constituent of *Curcuma longa* has reported antiinflammatory activity which has low absorption from GIT as it is rapidly metabolized. By using different polymer blends the amount of drug in the body may increase and increase the antiinflammatory activity. It can be concluded that increase in the hydrophilic polymer content leads to increase in the flux through unit cross sectional area and in moisture content which would maintain the integrity of formulation with general skin folding. Formulation F-4 overall shows better results as compared to other formulations so it can be concluded that a right combination of hydrophilic and hydrophobic polymers is compulsory for better results. Use of curcumin in TDDS can be also considered as a new version of technically improved method of ayurvedic turmeric *poultice* or *lepa*.

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