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Formulation and evaluation of transdermal patches of curcumin

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ABSTRACT

An attempt was made to formulate and evaluate the curcumin transdermal drug delivery system. Preformulation studies on the drug curcumin were done which included description, solubility and compatibility studies. The transdermal patches were made which were of matrix diffusion control system. Solvent casting technique was used to prepare the transdermal patches. Three formulations were made with 20mg of curcumin and by using polymers namely hydoxy propyl methyl cellulose, ethyl cellulose at various ratios and the yield was noted. Curcumin was physically examined for color and odour. Solubility was determined in water, phosphate buffer pH -7.4, Ethanol, DMSO and Tetra hydro furan. Interaction of drug and polymer was confirmed by UV – Visible interaction and FTIR studies. Based on this further evaluation was carried out.Invitro drug diffusion stuy was also carried out using modified Franz diffusion cell. Transdermal patches were evaluated for the weight, thickness, percentage moisture uptake, percentage flatness, folding endurance, water vapor transmission rate, and in-vitro release studies. This was done for three formulations F1, F2, F3. It was found that formulation F1 showed the best compatibility on the basis of all tests performed.

Key words: Transdermal patches, Curcumin, Formulation.

INTRODUCTION

During the last two decades, significant advances have been made in the controlled release drug delivery of therapeutic agents. In the early stages of research on controlled release drug delivery, major emphasis was focused on the development of zero order release devices. Current technology has improved to such a level that delivery of some drugs at a constant rate for certain period of time ranging from days to years is not a major issue anymore.[1] Transdermal patches deliver drugs at a constant rate for 24 hours or longer and the Norplant system releases progestin levonorgestel from silicon rubber tubular capsules for several years. The promise of zero order release is to maintain a constant drug concentration in blood for an extended period of time. The zero order release of a drug, however, does not necessarily result in a constant drug concentration in blood. The absorption of the drug by the body usually does not follow the zero order kinetics, except when the drug is directly delivered into the blood stream by an infusion

pump.[2] The nonzero order drug absorption is still effective in most cases as long as the drug concentration is maintained between the minimum effective and maximum safe concentrations. The drug delivery needs to be feedback controlled depending on the drug concentration in blood pharmacologic effect. In many situations, drug needs to be released only when the body requires it. For example, insulin is required only when the glucose concentration in the blood is increased. Once the glucose level is decreased, no further insulin is required. The term controlled release has a meaning that goes beyond the scope of sustained drug action. It implies a predictability and reproducibility in the drug release kinetics , which means that the release of drug ingredients from a controlled release drug delivery system proceeds at a rate profile that is not only predictable kinetically, but also reproducible from one unit to another.[3]

Treatment of illness through medication has entered an era of rapid growth. History reveals that topical application of drugs has been an ancient practice as evidenced by application of ointments on various parts of the body for various purposes. Now a days also a range of topical preparations like ointments, creams etc are used. Theoretically drugs can be applied topically as powders, sprays or solutions. [4]The topical preparations generally carry drugs for local action on the tissues near the site application. However, recently the skin has been increasingly employed for sustained delivery systems, easy to apply and afford precise modulation of the rate of drug entry into the systemic circulation. Through such drug delivery excessive dumping of the drug into the blood, otherwise associated with other dosage forms, can be minimized. Poor patient compliance is a frequent problem in daily clinical practice with other dosage forms i.e. oral dosage forms or IV or IM dosage forms etc.[5,6] The unfavorable pharmacokinetic of the drug, the inconvenience of the standard form of such drug application and the side effects due to the administration route often are the reasons of poor patient compliance. Delivery via the transdermal route is an interesting option in this respect because transdermal route is convenient and safe.[7] This offers several potential advantages over conventional routes like avoidance of first pass metabolism, predictable and extended duration of action, minimizing undesirable side effects, utility of short half-life drugs, improving physiological and Pharmacological response, avoiding the fluctuation in drug levels, inter and intra-patient variations and most importantly, it provides patient compliance as the drug delivery is painless.[8] Transdermal therapeutic systems are defined as self-contained, discrete dosage forms which, when applied to the intact skin, deliver the drug(s), through the skin, at a controlled rate to the systemic circulation[9.10]

Curcumin is capable of scavenging oxygen free radicals such as superoxide anions and hydroxyl radicals, which are the initiators of lipid per oxidation. [11]The lipid per oxidation has a main role in the inflammation, in heart diseases, and in cancer.[12,13] It was demonstrated that, curcumin protects (52%) hemoglobin from nitrate-induced oxidation to methemoglobin at 400 mM concentration. It has been suggested that the presence of a hydroxyphenyl group in compounds analogous to curcumin, especially in the 2-position, is supportive of the chemo protective activity through the ability to induce Phase II detoxification enzymes, so it has anticancer activity. Curcumin appear to reduce its anti-inflammatory activity by suppressing activation of NF-kB through inhibition of IkB kinase activity. An early study pointed to the fact that the hydroxyphenyl unit in curcumin confers anti-inflammatory activity[14,15]

MATERIALS AND METHOD

Methods

1. Preformulation studies

It is one of the important prerequisite in development of any drug delivery system. Preformulation studies were performed on the drug, which included solubility and compatibility studies.

A. *Description*

Curcumin was physically examined for colour and odour etc.

B. *Solubility*

Solubility of curcumin was determined in water, phosphate buffer 7.4, ethanol, DMSO, tetra hydro furan, etc.

C. *Interaction Studies*

a. ***Drug-polymer interaction study***

Interaction of drug with polymers was confirmed by UV-visible interaction studies. The pure drug along with polymer was subjected to UV-visible studies.

D. *Preparation of standard curve for curcumin*

Primary stock solution

100 mg of curcumin was accurately weighed and dissolved in 30 ml ethanol and diluted to 100 ml with distilled water.

Secondary stock solution

1 ml of primary solution was diluted to 100 ml distilled water to get a concentration of 10 mcg /ml. From these 1 ml was pipette out diluted to 10 ml to get a concentration of 1 mcg/ml. Aliquots of 1 ml, 2 ml, 4 ml, 6 ml, 8 ml, and 10 ml were pipette out and diluted to 10 ml with distilled water to get a 1 mcg, 2 mcg, 4 mcg, 6 mcg, 8 mcg, and 10mcg concentration of curcumin. Standard graph was plotted by keeping the known concentration on X-axis and obtained absorbance on Y-axis.

E. *Preparation of sodium lauryl sulphate solution*

Accurately weighed500mg of sodium lauryl sulphate and transferred into 100ml standard flask. Dissolved with distilled water and finally made up the volume.

2. *Preparation of Transdermal patches*.

Solvent casting technique

The Transdermal patches prepared are of matrix diffusion controlled systems. Solvent casting technique was used to prepare the transdermal patches.

Procedure

Preparation of F1 patch

Accurately weighed 1gm HPMC and 1gm EC and dissolved in 10ml of distilled water and 10ml 0f ethanol respectively.

Preparation of F2 patch.

Accurately weighed 1gm HPMC and 0.5gm EC and dissolved in 10ml of distilled water and 10ml 0f ethanol respectively.

Preparation of F3 patch. Accurately weighed 0.5gm HPMC and 1gm EC and dissolved in 10ml of distilled water and 10ml 0f ethanol respectively. From the above each solution mixed 9ml HPMC solution and 1ml of EC solution separately. Added 2-3 drops of glycerin to each mixture and mixed well. Dissolved 20mg curcumin in 10ml ethanol and poured in to each mixture with continuous stirring with the help of magnetic stirrer. Poured each mixture into separate petridishes and allowed to stand for 24 hrs.

Evaluation of Transdermal patches

The prepared curcumin transdermal patches were evaluated as mentioned below.

1. Weight of the patch
2. Thickness of the patch
3. Percentage Moisture content
4. Percentage Moisture uptake
5. Percentage flatness
6. Folding endurance
7. Water vapour transmission rate
8. In vitro drug release studies

1. Weight of the patch

Three patches from each batch were taken and weight of each patch was found by using electronic balance. Then average weight of single patch was determined.

Table-I Weight of patch

Batch	Weight in mg	Mean
F1	263.40	275.11
	282.61	
	279.32	
F2	232.16	253.27
	259.23	
	268.41	
F3	248.39	252.39
	252.89	
	255.89	

2. Thickness of the patch

The thickness of the patch was assessed by using screw gauge at different points of the patch. From each formulation three randomly selected patches were used. The average value for thickness of a single patch was determined.

3. Percentage moisture content.

The prepared films were weighed individually and kept in a desiccator containing fused calcium chloride at room temperature for 24 hours. The film was again weighed and the percentage moisture content was calculated using the formula:

Percentage moisture content = [initial weight – final weight / final weight] × 100.

Table -II- Thickness of patch

Batch	Thickness in mm	mean
F1	0.183	0.162
	0.161	
	0.142	
F2	0.171	0.169
	0.189	
	0.149	
F3	0.118	0.116
	0.121	
	0.108	

Table -III: Percentage moisture content

Sl No	Initial weight	Final weight	% moisture content
F1	1.8024	1.6422	9.76%
F2	1.6310	1.4820	10.05%
F3	1.4164	1.3236	7.01%

4. Percentage moisture uptake

The weighed films were kept in a desiccator at room temperature for 24 hours and then exposed to 84 % relative humidity using a saturated solution of potassium chloride. Finally, the films were weighed and the percentage moisture uptake was calculated using the formula: percentage moisture uptake = [final weight-initial weight / initial weight] × 100.

Table -IV 3. Percentage moisture uptake

Sl. No	Initial weight	Final weight	% moisture uptake
1	1.24114	1.2821	3.28
2	1.4629	1.4969	2.32
3	1.1276	1.1623	3.08

5. Percentage flatness

Longitudinal strips cut out from each film, one from the Centre and two from the either side the length of each strip without applying an additional pressure was measured and the variation in length because of non uniformity in flatness was measured by determining percent constitution equivalent to 100%

Table- V: Percentage flatness

Sl No	Initial length (cm)	Final length (cm)	% flatness
F1	6.1	6.1	100
F2	6.3	6.35	99.99
F3	5.9	5.9	100

6. **Folding Endurance**

The number times the films could be folded at the same place without breaking gave the value of folding endurance. It was expressed a number of times. The patches were folded at same place either to break the patches or to develop visible curves. It was done normally for the prepared

(Table-VI) Folding endurance

Serial number	Thickness in mm	Folding endurance
F1	0.426	> 100
F2	0.394	>150
F3	0.358	>150

7. Water vapor transmission

The film was fixed over the glass vial with an adhesive containing 1 g of fused calcium chloride as a desiccant. Then, the vial was placed in desiccator containing saturated solution of potassium chloride (relative humidity 84 %). The vial was taken out periodically and weighed.

(Table –VII) Water vapor transmission
Water vapour transmission (g / cm ^{2} / h)

BATCHES	24h	48h	72h	96h
P1	0.0006	0.0016	0.0027	0.0041
P2	0.0012	0.0026	0.0038	0.0049
P3	0.0009	0.0021	0.0033	0.0046

8. **In vitro drug release studies**

a) In-vitro Drug Release

The fabricated film was placed on the egg membrane and attached to the diffusion cell such that the cell's drug releasing surface towards the receptor compartment which was filled with 50 ml of sodium lauryl sulphate solution at 32±1^{0}C. The elution medium was stirred magnetically. The aliquots (5ml) were withdrawn at predetermined time intervals and replaced with same volume of sodium lauryl sulphate solution. The samples were analysed for drug content using UV spectrophotometer at 429nm.

(Table -VIII) Drug permeation through egg membrane: Receptor compartment containing SLS solution with distilled water for F1

Time	Square root of time	Log (time)	Cumulative Amount Release	% Cumilative amount released	Log cumulative % drug released	% of drugs remaining in matrix	Log % of drug remaining in matrix
0.5	0.70	-0.30	0	_____	-	100	2
1	1	------	0.20.10	2.39	0.37	99.79	1.99
2	1.41	0.30	0.62	7.40	0.86	99.37	1.99
3	1.73	0.47	1.19	14.20	1.15	98.80	1.99
4	2	0.60	1.98	23.60	1.37	98.01	1.99
5	2.23	0.69	3.00	35.75	1.55	96.99	1.98
6	2.44	0.77	4.16	49.67	1.69	95.83	1.98
7	2.64	0.84	5.42	64.57	1.81	94.57	1.97
8	2.82	0.90	6.90	82.20	1.91	93.09	1.96

(Table : IX) Drug permeation through egg membrane: Receptor compartment containing SLS solution with distilled water for F2

Time	Square root of time	Log (time)	Cumulative Amount Release	% Cumilative amount released	Log cumulative % drug released	% of druge remaining in matrix	Log % of drug remaining in matrix
0.5	0.70	-0.30	0	_____	-	100	2
1	1	------	0.15	1.64	0.21	99.84	1.99
2	1.41	0.30	0.66	7.26	0.86	99.33	1.99
3	1.73	0.47	1.26	13.74	1.13	98.73	1.99
4	2	0.60	1.96	21.36	1.32	98.03	1.99
5	2.23	0.69	2.82	30.69	1.48	97.17	1.98
6	2.44	0.77	3.93	42.75	1.63	96.06	1.98
7	2.64	0.84	5.25	57.10	1.75	94.74	1.97
8	2.82	0.90	6.81	74.06	1.86	93.18	1.96

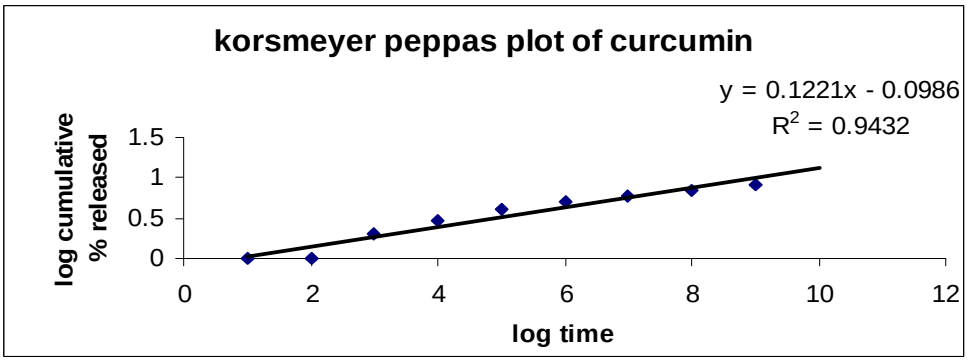
(Table-X) Drug permeation through egg membrane: Receptor compartment containing SLS solution with distilled water for F3

Time	Square root of time	Log (time)	Cumulative Amount Release	% Cumulative amount released	Log cumulative % drug released	% of drugs remaining in matrix	Log % of drug remaining in matrix
0.5	0.70	-0.30	0		-	100	2
1	1	------	0.19	1.88	0.27	99.81	1.99
2	1.41	0.30	0.64	6.42	0.80	99.35	1.99
3	1.73	0.47	1.23	12.19	1.08	98.76	1.99
4	2	0.60	1.93	19.13	1.28	98.06	1.99
5	2.23	0.69	2.87	28.47	1.45	97.12	1.98
6	2.44	0.77	4.09	40.53	1.60	95.90	1.98
7	2.64	0.84	5.38	53.30	1.72	94.61	1.97
8	2.82	0.90	6.89	68.27	1.83	93.10	1.96

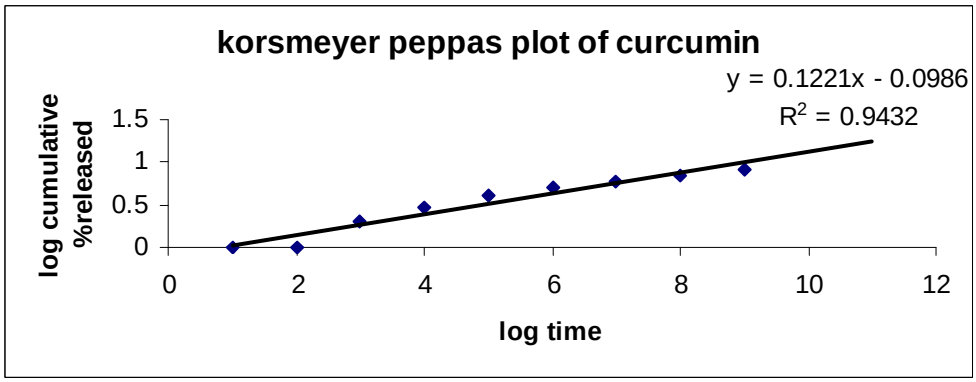
d) Kinetics of drug release

To examine the drug release kinetics and mechanism, the cumulative release data were fitted to models representing zero order (Q v/s t), first order [Log(Q_0-Q) v/s t], Higuchi's square root of time (Q v/s $t^{1/2}$) and Korsemeyer Peppas double log plot (log Q v/s log t) respectively, where Q is the cumulative percentage of drug released at time t and (Q_0-Q) is the cumulative percentage of drug remaining after time t.

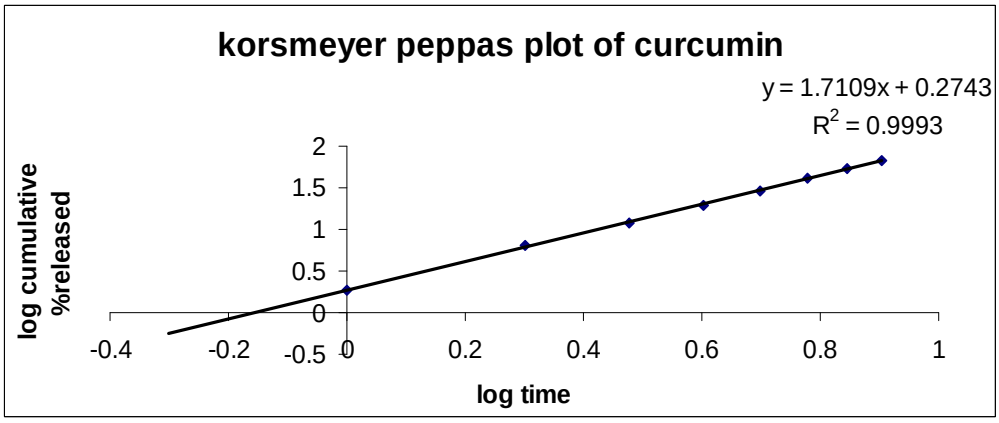
Graph . I korsmeyer- peppas plot of curcumin



Graph .II korsmeyer-peppas plot of curcumin



Graph III korsmeyer-peppas plot of curcumin.



RESULTS & DISCUSSION

Preformulation Studies

1. Description

Curcumin was physically examined for colour and odor etc. It is a orange yellow powder, with characteristic odour.

2. Solubility

Curcumin was insoluble in water, poorly soluble in buffer solution pH 7.4, and soluble in ethanol, DMSO, and Tetrahydro furan (THF).

3. Interaction Studies

a. Drug-polymer interaction study in uv-visible

Interaction of drug with polymers was confirmed by carrying out UV-Visible interaction studies. The UV-Visible overlay spectrum of drug alone and drug with polymer were seen. It shows that there are no interactions found between the drug and polymers.

b. Drug-polymer interaction study FTIR

Interaction of drug with polymers was confirmed by carrying out IR interactions studies. The IR overlay spectrum of drug alone and drug with polymer were seen. It shows that there are no interactions found between the drug and polymers.

CONCLUSION

Transdermal patches of curcumin were prepared by the synthetic polymers combination of Hydroxy propyl methylcellulose (HPMC) and Ethyl cellulose (EC). The patches were transparent, smooth and flexible. . The solubility studies show that curcumin has very good solubility in ethanol, Tetra hydro furan, and DMSO. The UV-Visible interaction studies indicate that there is no interaction found between the drug and polymers. Among the various batches, the uniformity weight and thickness indicates that the polymeric solution of the drug is well dispersed in the patches.

However the moisture absorbed did not affect adversely the patch strength and integrity. The small moisture content helps them to remain stable and protect from being a completely dried and brittle patches. The % flatness indicates the physical integrity of the patch was excellent and folding endurance reveals the very good flexibility of the patch. The water vapour transmission studies indicated that all the films were permeable to water vapour. Water vapour transmission through the films followed zero order kinetics.The invitro permeation studies of patches using egg membrane as barrier was carried out using 0.5% sodium lauryl sulphate solution in the receptor compartment with three different patches, F1, F2 and F3 using HPMC and EC in the concentration ratio of 1:1, 1:0.5 and 0.5:1 respectively. Results of invitro permeation studies shows that 1:1 concentration ratio of HPMC and EC bring the satisfactory release of curcumin. The cumulative percentage drug release of patch F1- 82.20%, F2- 74.06%, and F3-68.27%.The release kinetics was evaluated by making by use of zero order, first order, Higuchi's diffusion and Korsemeyer - Peppas equation. The drug release through the transdermal patches of curcumin following zero order kinetics. The n value for korsemeyer - peppas equation for patch no: F1 and F2 suggests that release mechanism following Fickian diffusion and that of F3 suggests that release mechanism following case 2 relaxation or super case transport 2.

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