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TRANSDERMAL PATCH INCORPORATING HERBAL BIOACTIVE INGREDIENTS: SYNTHESIS, OPTIMISATION & EVALUATION

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ABSTRACT
Drug delivery systems (DDS) are formulations that allow the introduction of therapeutic substances into the body and improve their efficacy and safety by regulating the rate, time, and location of drug release. The term "drug carrier" refers to any substrate used in the delivery of drugs in order to improve their selectivity, effectiveness and safety. Formulation were evaluated for its Physicochemical characteristic such as particle size, Polydispersity index, zeta potential and also evaluated for entrapment efficiency, Drug content, In vitro drug release study.

Keywords: Curcumin, Herbal, Transdermal Drug Delivery System, Transdermal Patches.

INTRODUCTION

Drug delivery systems (DDS) are formulations that allow the introduction of therapeutic substances into the body and improve their efficacy and safety by regulating the rate, time, and location of drug release. In order for the drug to be delivered to the patient, it must be delivered by a drug delivery system. In some cases, the drug is formulated in a way to allow it to be administered to a patient for a therapeutic purpose or it can be used to deliver the drug [1].

A drug's pharmacological properties play an important role in the physiological effects that are caused by the drug when it is taken by a patient. It is generally the case that these biological effects are produced by an interaction between the drug and specific receptors at the site of action of the drug that results in these effects. In spite of this, unless the drug can be delivered to the target site of action at a level and concentration that minimizes side effects while maximizing therapeutic effects, there is a risk that their efficiency will be compromised. A good drug candidate may not be able to be used in certain cases because of delivery and targeting challenges that are so great that they prevent the drug candidate from being effective.

Depending on how a drug is delivered, its efficacy may be significantly affected by the method by which it is delivered. In some drugs, there is an optimal concentration range within which the maximum benefit will be derived, and concentrations above or below this range can have a toxic effect, or can provide no therapeutic benefit at all. However, the very slow progress in the efficacy of the treatment of severe diseases has suggested that a multidisciplinary approach is needed to deliver therapeutics to specific targets in tissues, in light of the very slow progress in the efficacy of the treatments of severe diseases. It is this knowledge that has led to the generation of new ideas on how to control pharmacokinetics, pharmacodynamics, non-specific toxicity, immunogenicity, biorecognition, and efficacy of drugs. In recent years, polymer science, pharmaceutics, bioconjugate chemistry, molecular biology, and polymer science have been combining their efforts into new drug delivery approaches that are often referred to as drug delivery systems (DDS) [2].

Advantages of TDDS

1. Avoid intravenous dangers and oral absorption and metabolism issues.
2. TDDS's continuous drug administration allows the use of short-half-life drugs.
3. Transdermal medication administration enhances bioavailability, reducing daily dose.
4. No first-pass hepatic metabolism.
5. Reduce GI symptoms [3].

Preformulation Study:

- **Organoleptic Characteristics of Curcumin**

➢ Physical examine was done to check Organoleptic Characteristics of curcumin like colour and odour.

- **Solubility study**

➢ Solubility of the curcumin can be done by using various solvents according to the standard procedure.

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- **Standard calibration curve graph of curcumin**

➢ 100mg of curcumin was dissolved in 10 ml of ethanol and made up to the volume with pH 7.4 phosphate buffer.

➢ From this stock solution (100µg/ml), a series of concentrations 2, 4, 6, 8, 10, 12µg/ml was prepared and the samples were scanned using UV-spectrophotometer. The maximum wavelength was found to be at 425 nm. The absorbance was noted at 425 nm using UV spectrophotometer and the graph were plotted with concentration on X axis and absorbance on Y axis [4].

Formulation Of Transfersomes

There are various methods for the preparation of transfersomes,

Thin film hydration method, Vortexing sonication method, Ethanol injection method, Modified handshaking method, Suspension homogenization method, Centrifugation method, Reverse phase evaporation method, High pressure homogenization technique.

Selection Of Method Of Preparation

➢ The method that was selected for further studies depended upon maximum drug content and least particle size [5].

Ethanol Injection Method

➢ The organic phase is produced by dissolving the phospholipids, edge activator, and the lipophilic drug in ethanol with magnetic stirring for the respective time, until a clear solution is obtained.

➢ The aqueous phase is produced by dissolving the water soluble substances in the phosphate buffer. The hydrophilic drug can be incorporated.

➢ Both solutions are heated up to 45-50^{o}C. Afterwards, the ethanolic phospholipid solution is injected drop wise into the aqueous solution with continuous stirring for the respective time.

➢ Ethanol removal is done by transferring the resultant dispersion into a vacuum evaporator and then sonicated for particle size reduction [6].

Other methods

High-Pressure Homogenization Technique

➢ The phospholipids, edge activator and the drug are uniformly dispersed in PBS or distilled water containing alcohol and followed by ultrasonic shaking and stirred simultaneously.

➢ The mixture is then subjected to intermittent ultrasonic shaking. The resulting mixture is then homogenized using a high-pressure homogenizer. Finally, the transfersomes are stored in appropriate conditions [7].

Centrifugation Process

➢ The phospholipids, edge activator and the lipophilic drug are dissolved in the organic solvent. The solvent is then removed using a rotary evaporator under reduced pressure at the respective temperature.

➢ The remaining traces of solvent are removed under vacuum. The deposited lipid film is hydrated with the appropriate buffer solution by centrifuging at room temperature. The hydrophilic drug incorporation can be done in this stage.

➢ The resulting vesicles are swollen at room temperature. The obtained multilamellar lipid vesicles are further sonicated at room temperature [8].

Characterization Of Transfersomal Formulation

Particle Size and Polydispersity Index

The particle size and poly dispersity index of transferosome formulation was measured at 25^{o}C using a computerized zeta sizer instrument. Transfersomal formulation in zeta sizer cell and the particle size is measured.

Zeta Potential

The electrophorotic mobility (zeta potential) of transfersomal dispersions was analyzed using zeta sizer and the values were obtained. The zeta potential values were within the standard values. The zeta potential was measured by Zeta sizer at 25^{o}C. The samples were kept in the polystyrene cuvette and a zeta dip cell was used to measure the zeta potential. If the zeta potential of the formulations is >0 or <30 mv, it is assumed that the formulations are stable without any aggregation.

The zeta sizer capillary cell was cleaned with 90% ethanol and distilled water before analysis. The measurement was performed at 25^{o}C after an appropriate dilution with distilled water. All of the measurements were repeated at least three times and zeta potential was determined as a mean ±SD.

Entrapment Efficiency

The entrapment efficiency of transfersomal suspension was estimated by centrifugation method. Transfersome suspension was taken and placed in centrifugation tube which is centrifuged at 15,000 rpm for 45 mins. Supernatant was withdrawn and diluted with phosphate buffer 7.4. The solution was analysed by using UV spectrophotometer at 425 nm. Entrapment efficiency is expressed as the percent of drug entrapped.

$$\% \text{ Entrapment efficiency} = \frac{\text{Total drug} - \text{Unentrapped drug}}{\textit{Total drug}} \times 100$$

Drug Content

The drug content of transfersomal formulation was determined by mixing the formulation with methanol and sonicated for 20 minutes to obtain a clear solution and filtered. The filtrate was analysed for drug content by UV at wavelength 425 nm.

Invitro Drug Release Studies

In vitro release of curcumin bearing transfersomes was determined using dialysis membrane. Transferosome suspension equivalent to 8 mg drug was filled in dialysis membrane and the ends are sealed with clamps and

immersed in a beaker containing 200ml of phosphate buffer (pH7.4) which was maintained at 32°±2°C which is constantly stirred at 100 rpm over a magnetic stirrer.

Samples of 2.5 ml were withdrawn from the receptor compartment at predetermined intervals(1,2,3,4,5,6,7,8,9,10,11,12,24hrs) and immediately replaced with fresh buffer to maintain the sink condition throughout the experiment. The samples were analysed at 425 nm by using UV spectrophotometer [9].

Formulation Of Patch

Prepation Of Transdermal Patch

Transdermal patch is developed by using solvent evaporation method. Hydroxy propyl methyl cellulose was dissolved in ethanol and maintained at the magnetic stirrer till it reaches semisolid consistency. Drug in the form of transfersomal suspension is incorporated into these solvents and stirred continuously. Glycerol should be added drop by drop as a plasticizer. Then it can be poured into petridish and place the inverted funnel on it and allow it to dry for 24 hrs to yield a patch.

After 24 hours, the patches were removed by using sharp knife by inserting along the edge of the patch and stored for further studies [10].

Evaluation Of Transdermal Patch

Physical Appearance

Prepared patches were visually inspected for colour, clarity, flexibility, and smoothness.

Thickness and Weight Variation

The thickness of the patches was assessed at three different points using micrometer screw gauze. Three patches were weighed individually and average weight of three patches was determined.

Folding Endurance

Patch was repeatedly folded at the same place till it broke. The number of times the film could be folded at the same place without breaking gives the value of the folding endurance.

Percentage Moisture Content

The prepared patches were weighed individually and kept in a dessicator containing fused calcium chloride at room temperature for 24 hrs. After 24 hrs the patches were reweighed and the percentage moisture content was determined.

$$\%\ Moisture\ content = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

Percentage Moisture Uptake

The weighed patches were kept in a desiccator at room temperature for 24 hrs containing saturated solution of potassium chloride in order to maintain 84% RH. After 24 hrs the patches were reweighed and the percentage moisture uptake was determined.

$$\%\ Moisture\ content = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

Drug Content

Small circular patch were cut out and soaked in 100ml of PBS pH 7.4 and allow it to 24 hrs and measured using UV spectrophotometer at 425 nm after 24 hrs.

Flatness

The flatness test was conducted using circular patch which was prepared were cut down into three longitudinal strips and measured the uniformity of flatness.

Invitro Drug Release Study Of Patch

The *in vitro* drug release study of patch is performed by using open ended tube. One end of the tube is tied with the dialysis membrane and the prepared transdermal patch is placed over the dialysis membrane. The receiver medium is filled with the freshly prepared phosphate buffer pH7.4 and the media was stirred to ensure the uniformity with a magnetic bead. At a predetermined time rate, 2.5 ml of the medium is withdrawn and the equal volume of fresh phosphate buffer was added to maintain the sink condition. Then the samples are evaluated and determine the absorbance using UV spectrophotometer and calculate the percentage of cumulative percentage drug release of patch [11].

Table 1: Formula of transfersomes formulation.

Formulation code	Drug (mg)	Soya lecithin	Tween 80 (mg)	Span 80 (mg)	Span 60 (mg)	Tween 40 (mg)	Ethanol: PBS pH- 7.4 (ml)
1	8	75	25	-	-	-	1:1
2	8	85	15	-	-	-	1:1
3	8	95	5	-	-	-	1:1
4	8	75	-	25	-	-	1:1
5	8	85	-	15	-	-	1:1
6	8	95	-	5	-	-	1:1
7	8	75	-	-	25	-	1:1
8	8	85	-	-	15	-	1:1
9	8	95	-	-	5	-	1:1
10	8	75	-	-	-	25	1:1
11	8	85	-	-	-	15	1:1
12	8	95	-	-	-	5	1:1

Table 2: Calibration curve of curcumin

CONCENTRATION (µg/ml)	ABSORBANCE
2	0.059±0.01
4	0.125±0.02
6	0.186±0.01
8	0.259±0.02
10	0.324±0.04
12	0.385±0.04

Table 3: Formulation of Transferosome

Formulation code	Drug (mg)	Soya lecithin	Tween 80 (mg)	Span 80 (mg)	Span 60 (mg)	Tween 40 (mg)	Ethanol: PBS pH- 7.4 (ml)
1	8	75	25	-	-	-	1:1
2	8	85	15	-	-	-	1:1
3	8	95	5	-	-	-	1:1
4	8	75	-	25	-	-	1:1
5	8	85	-	15	-	-	1:1
6	8	95	-	5	-	-	1:1
7	8	75	-	-	25	-	1:1
8	8	85	-	-	15	-	1:1
9	8	95	-	-	5	-	1:1
10	8	75	-	-	-	25	1:1
11	8	85	-	-	-	15	1:1
12	8	95	-	-	-	5	1:1

Table 4: Particle size and Polydispersity index.

Formulation code	Particle Size (nm)	Polydispersity Index
F7	236.6	0.599

Table 5: Zeta Potential.

Formulation Code	Zeta potential
F7	-14.1

Table 6: Entrapment Efficiency.

Formulation Code	Entrapment Efficiency % ±S.D
F1	60.59±1.05
F2	51.02±0.86
F3	57.32±1.15
F4	81.55±0.61
F5	76.35±0.99
F6	73.75±1.02
F7	88.32±0.74
F8	84.51±1.21
F9	79.73±0.79
F10	68.21±1.21
F11	70.09±0.64
F12	70.80±1.31

Table 7: Drug content (%)

Formulation Code	Drug content % ±S.D
F1	81.24±1.05
F2	84.25±0.86
F3	73.40±1.15
F4	79.12±0.61
F5	81.20±0.99
F6	73.86±1.02
F7	89.56±0.74
F8	81.21±1.21

F9	82.49±0.79
F10	76.08±1.21
F11	72.45±0.64
F12	77.89±1.31

Table 8: In vitro Drug release of Transferosomes.

Formulation Code	Percentage release of Drug
F1	44.28±0.32
F2	50.35±0.75
F3	48.05±0.29
F4	49.21±0.87
F5	42.06±0.19
F6	41.14±0.87
F7	59.21±1.25
F8	55.19±0.99
F9	51.70±0.32
F10	32.26±1.11
F11	38.8±0.75
F12	36.87±0.45

Table 9: Formulation of Patch.

S. No	Ingredients	Quantity
1	HPMC	300mg
2	PEG-400	150mg
3	Ethanol	Q.S
4	Glycerol	0.5 ml
5	Drug loaded transferosomes	3.5 ml

Table 10: Thickness of Patch.

S. No	Patch Area	Thickness
1	1	0.5 mm
2	2	0.4mm
3	3	0.5mm

Table 11: Drug content.

DRUG CONTENT		
Actual yield	**Theoretical yield**	**Drug content**
7.21	8	90.12%

Table 12: In vitro drug release study of Patch

Time in hrs	%Drug release
1	1.96±0.43
2	3.48±0.41
3	4.73±0.32
4	5.41±0.36
5	7.68±0.41
6	9.94±0.78
7	13.28±0.85
8	17.69±0.85
9	20.98±1.25
10	23.89±0.19
11	28.17±0.58
12	33.15±0.09

Figure 1: Formulation of transfersomes

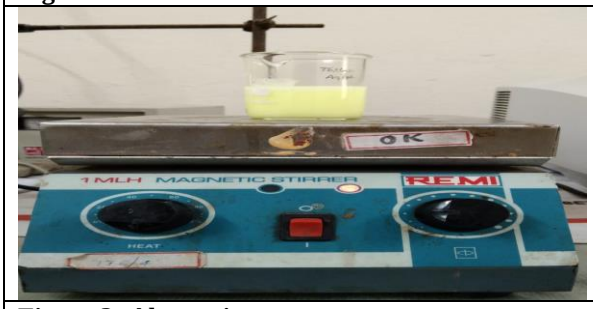


Figure 2: Curcumin transdermal patch

Figure 3: Absorption spectra

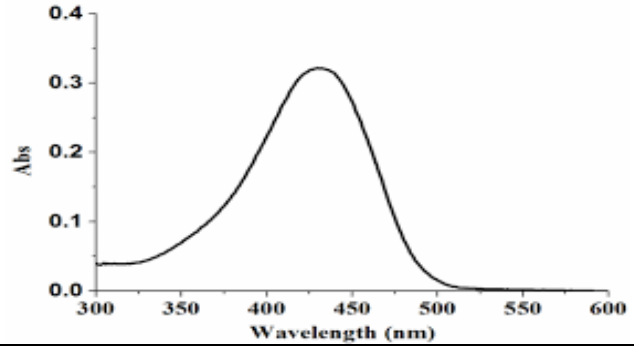


Figure 4: Calibration curve of curcumin

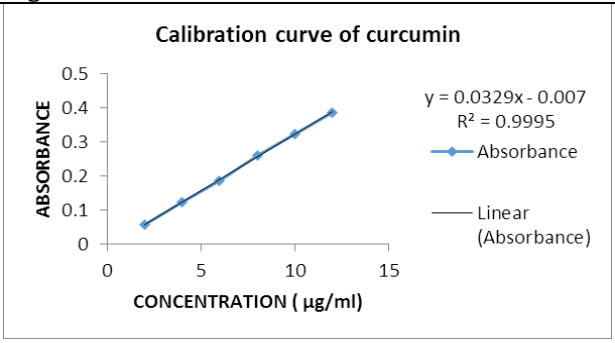


Figure 5: Particle size and polydispersity index

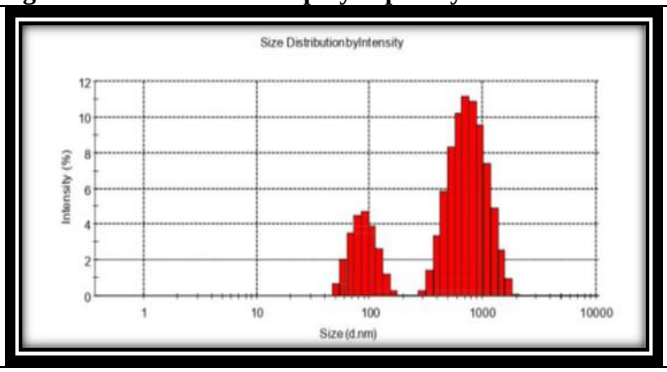


Figure 6: Zeta Potential

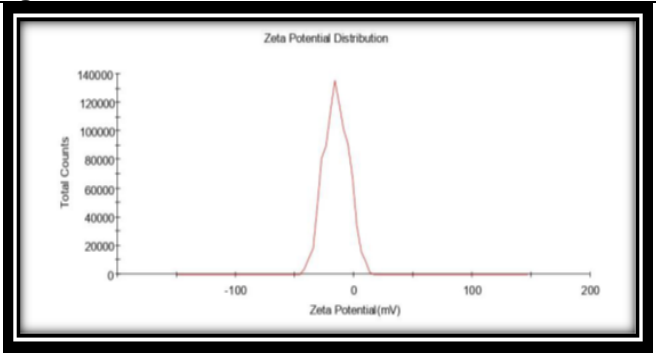


Figure 7: Entrapment Efficiency

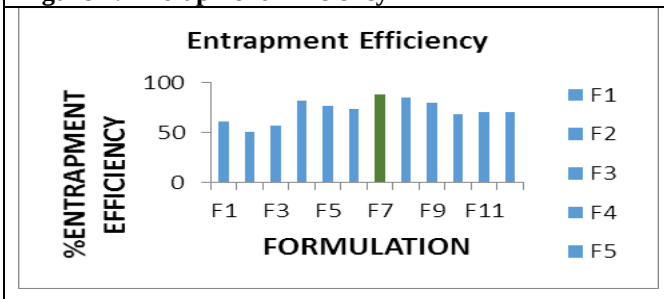


Figure 8: Drug content (%)

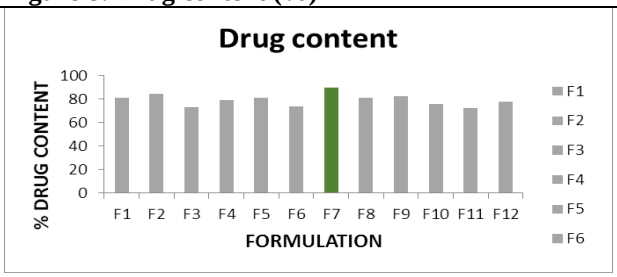


Figure 9: In vitro Drug release of Transferosome

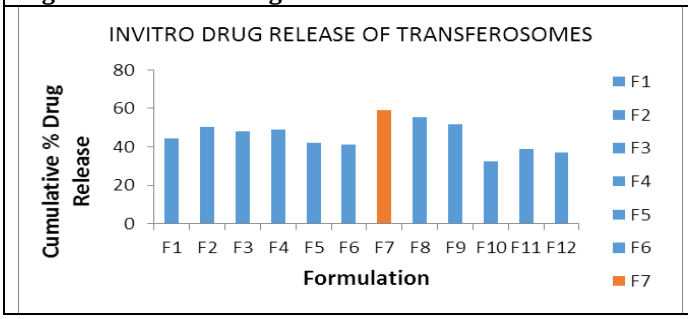
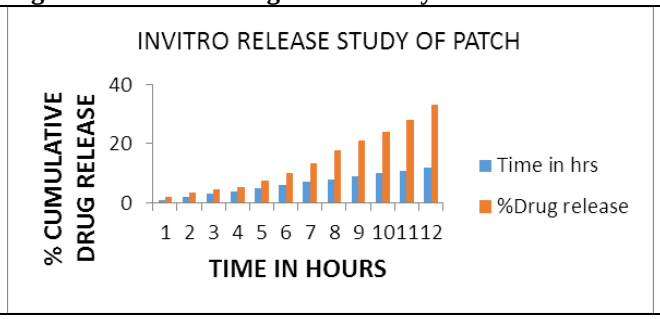


Figure 10: In vitro drug release study of Patch



Results And Discussion

Determination Of Wavelength

The λ max of curcumin was determined by scanning the solution with the concentration (10µg/ml) of drug in phosphate buffer pH 7.4 by UV spectrophotometer in the UV range of 200-800 nm and the peak at maximum wavelength was obtained and thus the λ max of drug was identified.

Preparation Of Calibration Curve

The calibration curve of curcumin drug was done by accurately weighing 100mg of pure drug and it was dissolved with 15ml of ethanol and made up to the volume with phosphate buffer pH 7.4 which is stock- A , 10ml was taken from stock- A and made up to 100 ml using phosphate buffer 7.4 which is stock- B.

From this dilution, 2, 4, 6, 8, 10, 12 µg/ml were made accordingly using phosphate buffer pH 7.4 and the regression value was found to be 0.9995. The values of calibration were shown in table 3 and the image was shown in figure 12.

Solubility Studies

The solubility of Curcumin was determined in various solvents and it was observed that the solubility of drug is better in ethanol when compared to other solvents.

Preparation Of Transfersomal Formulation

The transfersomal formulation was prepared using phospholipid and surfactant as edge activator. Twelve different batches were prepared by varying the concentration of phospholipid and surfactant. Phospholipid is dissolved in ethanol (organic phase) and then surfactant is added in the organic phase. Then the pure drug Curcumin was dissolved in phosphate buffer pH 7.4 (aqueous phase).

These solutions were maintained under magnetic stirrer at a constant temperature. Then the ethanolic phospholipid solution (organic phase) is drop wise injected into the aqueous phase with continuous stirring for respective time. Ethanol removal is done at room temperature and then the transferosome dispersion sonicated for particle size reduction.

Particle Size And Polydispersity Index

The particle size and poly dispersity index of transferosome was measured by the dynamic light scattering technique using a computerized zeta sizer instrument. Transfersomal formulation is filled in the zeta sizer call and measured for size. The particle size range of the formulation within the nanometric range. The average particle size of the optimized batch was found to be 236.6 nm and PDI is 0.599.

Zeta Potential

The 16lectrophoretic mobility (zeta potential) of transfersomal dispersions was analysed using zeta sizer and the values were obtained. The zeta potential values within the standard range. The values depict that the particle possess neutral charge owing to the usage of surfactants as edge activator and soya lecithin as phospholipid. The zeta potential of the formulation depicts the good stability of the vesicular formulation. If the zeta potential of the formulation is > or < 30mv it is assumed that the formulation are stable without any aggregation. If higher charge on the surface of the vesicles, that produced a repulsive force between the vesicles which made them stable and devoid of aggregation The values obtained here indicated that the formulation do not cause any aggregation due to the usage of the phospholipids and the surfactant. Hence the formulation (F7) was observed with -14.1 mV and found to better stable than other formulations.

Entrapment Efficiency

The entrapment efficiency of the formulation helps to identify the characteristics of drug, phospholipids and surfactant. It is identified for prepared formulations of transfersomes using refrigerator centrifuge method. Transfersomes were centrifuged for 1 hour at 15000 rpm. Supernatant containing unentrapped drug was separated and measured by a UV spectrophotometer at the $\lambda\, max$ of 425nm. The entrapped efficiency of all batches ranged from 51.02%-88.32%. F7 showed the maximum entrapment efficiency.

Drug Content

Drug loaded transfersomes were mixed with methanol and sonicated for 20mins to obtain a clear solution and determined spectrometrically a 425 nm. F7 has the greater content of drug in it has 89.56±0.74. It is suitable for the further studies hence it has a greater drug content.

Selection Of Best Formulation

For a good penetration across the skin, a compound should be in optimum particle size, with good entrapment efficiency and stability is also desirable. Taking this in consideration F7 formulation was found to the best formulation. It has a drug content of 89.56±0.74 and 88.32%±0.74 of entrapment efficiency and this is best suited for characterization studies.

In Vitro Drug Release Study

The release studies of transfersomal formulations were carried out using dialysis membrane. The drug release was found to be governed by lipid structure and properties. A maximum of 59.21%±1.25 of drug was released at the end of 24 hours indicating the sustainable delivery. This sustainable released could be due to the high entrapment of the lipophilic drug in the lipid matrix. Highest drug release has achieved by formulation F7 hence it is selected as a best formulation and used for further studies.

FORMULATION OF PATCH

The transfersomal patch was prepared using optimized formulation F7. It was loaded in the patch by calculating the amount of drug needed to be loaded as per the formula. HPMC and ethanol provided good consistency and Glycerol assisted in plasticizer activity. The

formulated patch was stored by packing in butter paper and wrapped in aluminium foil sheet.

PATCH CHARACTERIZATION

Physical Appearance

- Light yellowish in colour, Smoothness, Flexible.

Thickness Uniformity

By measuring the patch using calliper at three different areas thickness was calculated and from the results it indicates patch has better uniformity in terms of its thickness.

Folding Endurance

Number of folds either to break the patch or develop the visible cracks was measured in the forms of folding endurance. This test holds the importance of checking the ability of the patch to withstand folding. Number of times the patch could be folded at the same place without breaking indicates the value. Hence here by measuring the formulated patch by folding reveals that it has the ability of 76 times to withstand folding without breaking or visible damage of cracks.

Folding endurance = 71±13

Percentage Moisture Loss

By placing in desiccator loss of moisture was calculated by using the formula;

$$\%\ Moisture\ content = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

The percentage moisture loss was found to be 5.74%.

Percentage Moisture Uptake

By placing in desiccator absorption of moisture was calculated by using the formula;

$$\%\ Moisture\ content = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

The percentage moisture uptake or moisture absorption was found to be 4.29%. The lower moisture content in the patch helps them to remain stable and become completely dried and brittle patch. It protects it from microbial growth.

Drug Content

Percentage content of the drug was calculated in the prepared patch by soaking it overnight in buffer and after 24 hours it was measured UV spectrophotometrically at 425 nm.

Flatness

Prepared patch were cut down into three longitudinal strips in three different areas and uniformity was measured. It ensures that prepared patch has considerable flatness uniformity.

In Vitro Drug Release Study

Amount of drug loaded was calculated to formulate a patch with ideal dose in a small circular area. After preparation of such patch, area of small circular patch was cut down and release study was carried out using dialysis membrane. The samples were collected and measured spectrometrically. From the results, graph was plotted by taking time in x-axis and cumulative drug release in y-axis. At the end of 12 hours drug release from the patch was found to be 33.15%±0.09.

Summary

A major objective of this study was to formulate and evaluate curcumin loaded transfersomes. Transfersomes were prepared by ethanol injection method using magnetic stirrer. It was formulated by using phospholipid (soya lecithin), edge activator such as Tween 80, Span 80, Span 60 and Tween 40.

The prepared transfersomes from F1 to F12 formulation were evaluated for its Physicochemical characteristic such as particle size, Polydispersity index, zeta potential and also evaluated for entrapment efficiency, Drug content, Invitro drug release study.

Further by using the optimized formulation, transdermal patch was prepared by the calculation of area of drug loading as per dose of the drug. Formulation F7 was loaded in a patch containing HPMC, Ethanol, PEG 400 and Glycerol. These patches were evaluated for physical appearance, thickness uniformity, folding endurance, percentage moisture absorption, percentage moisture loss, percentage drug content, flatness test, *in vitro* drug release study. Lesser value helps to maintain the stability and protects from microbial growth. Drug content was calculated and the % drug content was found to be 90.12% in the patch. Flatness test ensures the uniformity of the prepared patch. After the release these data were useful for further studies.

Conclusion

In this novel approach, active constituent curcumin transdermal patches were produced by ethanol injection method using various excipients. Although Transdermal systems provide a promising route of delivery for new age drugs, conventional and new dosage forms are equally essential for other drugs to increase their therapeutic efficacy. The patented innovations of TDDS focus on these parameters to make dosage form more patients complied and site specific delivery of the drug. More over *in vivo* performance of the dosage form specifies the ultimate test for the therapeutic efficacy of the drug.

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