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DESIGN AND COMPARISON OF EMULGELS PREPARED USING VARIOUS POLYMERS LOADED WITH PIPERINE DRUG

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ABSTRACT
The alkaloid piperine, found in black pepper, exhibits significant pharmacological properties, but is insoluble and unstable in water, making it challenging to administer topically. The purpose of this study was to develop and evaluate piperine-loaded emulgels using polymers in order to improve their topical delivery and therapeutic effectiveness. To determine whether different gelling agents impact the formulation characteristics and drug release profile of emulgels, Carbopol 940 and Hydroxypropyl Methylcellulose (HPMC) were used. Piperine was found to be compatible with the selected polymers and excipients in preformulation studies. Physical properties of the prepared emulgels, such as viscosity, spreadability, pH, and drug content uniformity, were evaluated to ensure they met acceptable standards. FTIR (Fourier Transform Infrared Spectroscopy) analyses confirmed the stability of piperine within the emulgel matrixes and the absence of significant interactions between the drug and polymer. Based on in vitro skin permeation studies, the optimized emulgel formulation provided enhanced transdermal delivery of piperine. The findings of this study demonstrate that the choice of polymer significantly impacts the physical properties and drug release profiles of piperine emulgels.

Keywords: Emulgel, Piperine, Carbopol 940, Hydroxypropyl Methylcellulose, Transdermal Delivery, Drug Stability.

INTRODUCTION

A well designed drug delivery system is as important as pharmacological activities of the drug for utilizing the benefits of the drug in an effective way. The drug should be delivered to the specific target site at a rate and concentration which are required for the optimal therapeutic efficiency and it should not be exposed to the other tissues so that the side effects can be minimized [1]. Inflammation is defined classically as a protective reaction by the body, in response to some physical or chemical injury. Acute inflammation is the body's initial response to a physical or chemical stress that requires healing and repair and is typically accompanied by pain, swelling, redness, and heat. Chronic inflammation is an abnormal condition that can cause or is associated with ill health and disease [2, 3].

Piperine is a member of Piperineoids isolated from spice turmeric which comes from the root curcuma longa (turmeric), a member of the ginger family, Zingaberaceae. Piperineoids include mainly Piperine (diferuloyl methane), demethoxyPiperine, and bisdemethoxycurcmin. Currently, it is one of the investigational new drug substance that has great clinical potential. It possesses diverse anti-inflammatory and anti-cancer properties following oral or topical administration. In Ayurveda (Indian traditional medicine), tumeric has been used for its medicinal properties for various indications and through different routes of administration, including topically, orally, and by inhalation. In vitro and animal studies have suggested Piperine may have antitumor, antioxidant, antiarthritic, antiamyloid, anti-ischemic, and anti-inflammatory properties [4 -14].

Topical drug delivery is intended for localized action on one or more layers of the skin. (e.g., sunscreens, keratolytic agents, local anesthetics, antiseptics and anti-inflammatory agents).

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Medication from these topical products does not reach the systemic circulation, even though if it reaches, it is usually in sub-therapeutic concentrations, and does not produce effects of any major concern except possibly in special situations, such as the pregnant or nursing patient. Skin is the primary target organ for topical delivery of the drug. The transportation and deposition of the drug within the layers of the skin is influenced by various factors including skin physiology, physicochemical properties of drugs and excipients, as well as fabrication and design of the delivery systems. The selection of formulation type is dependent on many factors including indication and patient acceptability, physiochemical properties of the active pharmaceutical ingredient (API), drug release, and stability issues, among others [15].

Emulgels are emulsions which are gelled by mixing with a gelling agent. The emulsion gels can also be described as hydrogels containing randomly distributed oil micro droplets. The release of the drug from the emulgels is influenced by the type of gelling agent and concentration of both the oily phase and emulsifying agent [16].

MATERIALS AND METHODS

Materials Used

Piperine, Carbopal 940, HPMC(K4M), Sodium alginate, Liquid paraffin, Propylene glycol, Tween 80, Span 20, Tween 20, Ethanol, Acetone.

Equipment Used

Fourier Transform Infrared Spectroscopy, Single pan digital balance, UV/visible spectrophotometer double beam, Magnetic stirrer, Mechanical stirrer.

METHODOLOGY

Construction of Calibration Curve for Piperine

Preparation of acetate buffer pH 5.5

Acetate buffer was chosen to simulate the human skin pH condition of 5.5. To prepare 1000 ml of the acetate buffer solution, 150 g of sodium acetate was dissolved in 250 ml of distilled water. Exactly 15 ml of glacial acetic acid was then added very slowly into the sodium acetate aqueous solution. Finally, the volume was made with distilled water.

Preparation of BTM releasing medium

Composition -
95% v/v acetate buffer
0.5% v/v tween 80
3% v/v methanol

Preparation of Standard Drug Solution

Stoke I solution: 100mg of Piperine was dissolved in 100 ml of acetate buffer p^H 5.5, so as to get a solution of 1000µg/ml concentration.

Standard solution: 10ml of stoke I solution was made to 100ml with acetate buffer p^H 5.5, thus giving a concentration of 100 g/ml. again 10ml of this stock II solution wasmade to 100ml with acetate buffer 5.5. Aliquot of standard drug solution ranging from 1 to 10 ml were transferred in to 10 ml volumetric flask and were diluted up to the mark with acetate buffer p^H 5.5. Thus the final concentration ranges from 1-10 g/ml. Absorbance of each solution was measured at 426.0 nm against acetate buffer p^H 5.5 as a blank. A plot of concentrations of drug versus absorbance was plotted. The linear regression analysis was done on absorbance data points. A straight-line equation was generated to facilitate the calculation of amount of drug.

Preformulation Studies

Before formulation of drug substances into a dosage form, it is essential that drug and polymer should be chemically and physically characterized. Preformulation studies give the information need to define the nature of the drug substance and provide a framework for the drug combination with pharmaceutical excipients in the fabricationof a dosage form.

Drug-excipient interaction study

This was carried out to check the compatibility between drug and various polymers. It is therefore necessary to confirm that drug is not interacting with polymers under experimental conditions and shelf life. In the present analysis it was carried out by FTIR analysis.

Fourier Transform Infrared Spectrophotometry (FTIR*)*

Compatibility study of drug with the excipients was determined by FTIR Spectroscopy. The pellets were prepared at high compaction pressure by using KBr and the ratio of sample to KBr is 1:100. The pellets thus prepared were examined and the spectra of drug and other ingredients in the formulations were compared with thatof the original spectra.

Methodology of Topical Piperine Emulgel

Emulgels are prepared by preparing the emulsion and its gellification by mixing withthe gel solution. Steps involved are:

Preparation of emulsion:

Oil phase was prepared by dissolving span 20 in liquid paraffin. Aqueous phase was prepared by the following steps. Tween 20 was dissolved in distilled water. Drug was dissolved in ethanol. Propyl and methyl parabens were dissolved in propylene glycol. Later two solutions were added to the former solution and mixed well.

Both the oil and aqueous phases are separately heated to 60-70^{0}C and then oil phase is added to the aqueous phase with continuous stirring. Stirring is continued until it reached the room temperature. Gel was prepared by simply dispersing the corresponding gelling agent indistilled water. Finally, the emulsion and the gel were mixed in 1:1 ratio with gentle stirring and the emulgel was obtained. The gel for formulaions F1, F2, F3, F4, was prepared by dispersing carbopol 940 in with constant stirring at moderate speed and after the addition ofemulsion, 1-2 drops of TEM (triethanolamine) was added and mixed thoroughly to get the final emulgel. The gel for the formulations F5, F6, F7, F8, was

prepared by disoarsingHPMC K4M in purified water and for F9, F10, F11, F12, was prepared by dispersing Na. alginate in purified water.

Evaluation of the Prepared Topical Piperine Emulgel
Physical appearance:

The prepared Piperine emulgel formulations were inspected visually for their color, homogeneity, texture.

pH determination: 1% aqueous solutions of the emulgels were prepared and the pHwas checked with a digital pH meter.

Consistency

This is done by using the consistency tester. One of the criteria for an emulgel to meetthe ideal quantities is that it should possess good spreadability which depends upon the consistency. It is term expressed to denote the extent of area to which gel readily spread on application to skin or affected part. The therapeutic efficacy of a formulation also depends upon its spreading value.

Spreadability:

Spreadability is expressed in terms of time in seconds taken by the slide to move fromA to B from 1gm of emulgel placed beneath the slides under the direction of certain load. Lesser the time taken for separation of two slides, better the spreadability.

Drug Content Determination

Drug concentration in emulgel was measured by UV spectrophotometer. Piperine content in emulgel was measured by dissolving 5ml quantity of emulgel in 100ml acetae buffer. Absorbance was measured after suitable dilution at 426 nm in UV/VIS spectrophotometer.

Model fitting for drug release

Drug release kinetics can be analyzed by various mathematical models, which are applied considering the amounts of drug released from 0 to 24 hour. Following equations presents the models tested. Depending on these estimations, suitable mathematical models to describe the dissolution profiles were determined. The following plots were made: cumulative % drug release versus time (zero-order kinetic model); log cumulative % drug remaining versus time (first-order kinetic model); cumulative % drug release versus square root of time (Higuchi model);

Zero order kinetic

Drug dissolution from pharmaceutical dosage forms that do not disaggregate and release the drug slowly (assuming that area does not change and no equilibrium conditions. are obtained) can be represented by the following equation:

$$Q1 = Q0 + K0t$$

Where Q is the amount of drug dissolved in time t, Q is the initial amount of drug in the solution (most times, Q 50) and *K* is the zero order release constant.

First order kinetics

The application of this model to drug dissolution studies was first proposed and later. This model has been also used to describe absorption and/or elimination of some drugs, although it is difficult to conceptualize this mechanism in a theoretical basis. The following relation can alsoexpress this model:

$$\ln Q_t = \ln Q_0 - k_1 t$$

Where Qt is the amount of drug released in time t, Q0 is the initial amount of drug in the solution and *K* is the first order release constant. In this way a graphic of the decimal logarithm of the released amount of drug versus time will be linear. The pharmaceutical dosage forms following this dissolution profile, such as those containing water-soluble drugs in porous matrices, release the drug in a way that is proportional to the amount of drug remaining in its interior, in such way, that the amount of drug released by unit of time diminishes.

Higuchi model

Higuchi (1961, 1963) developed several theoretical models to study the release of water soluble and low soluble drugs incorporated in semi-solid and/or solid. Mathematical expressions were obtained for drug particles dispersed in a uniform matrix behaving as the diffusion media. In a general way it is possible to resume the Higuchi model to the following expression

$$Q_t = K_H t_{1/2}$$

Where Qt is amount of drug released in time t and KH is release rate constants. Higuchi describes drug release as a diffusion process based in the Fick's law, square root time dependent. This relation can be used to describe the drug dissolution from several types of modified release pharmaceutical dosage forms, as in the case of some transdermal systems and matrix tablets with water soluble drugs.

Korsmeyer–Peppas model

developed a simple, semi empirical model, relating exponentially the drug release to the elapsed time (*t*). An equation that can be described in the following manner:

$$M_t / M_\infty = at^n$$

where a is a constant incorporating structural and geometric characteristics of the drug dosage form, n is the release exponent, indicative of the drug release mechanism, and the function of t is M /M (fractional release of drug). Peppas (1985) used this n value in order to characterize different release mechanisms, concluding for values for a slab, of n =0.5 for Fick diffusion and higher values of n, between 0.5 and 1.0, or n=1.0, for mass transfer following a non-Fickian model [17].

RESULTS & DISCUSSION

Based on the experimental methods, the results are arranged in the order of Construction of Calibration Curve for Piperine, FT-IR (Fourier Transform Infrared Spectrophotometry, Physical examination, pH determination, Consistency, Drug content determination,

Ex vivo diffusion study, Skin deposition study, and Skin Irritation test.

Construction of Calibration Curve for drug Piperine at λmax 426nm

The absorbances were measured by taking 1 µg/ml, 2 µg/ml, 3 µg/ml, 4µg/ml, 5µg/ml, 6µg/ml, 7µg/ml, 8µg/ml, 9µg/ml, 10 µg/ml as the serial concentrations spectrometrically at 426 nm. The Coefficient of Correlation (r^2) was found to be 0.994, slope was found to be 0.034 and the intercept was found to be 0.009.

FTIR (Fourier Transform Infrared Spectrophotometry)

The calibration curve was constructed for these values and this is found to be within the Beer-Lambarts Law.

Evaluation:

Physical Examination:

The prepared Piperine emulgel formulations were yellow viscous creamy preparations with a smooth and homogeneous appearance. pH testing, Consistency, Drug Content Determination :

Ex Vivo diffusion studies:

The release profiles of Piperine through the pig skin from its various emulgel formulations are represented as following.

Model Fitting Data For Drug Release

This is the kinetic model fitting data for the all emulgel formulations.

Skin irritation test:

The Primary Irritation Index of the test article was calculated and found to be zero.

Table 1: pH testing, Consistency, Drug Content Determination

Formulation	pH	Time taken forthe movement from A to B (sec)	Entrapment efficiency
F_1	6.5	5	85%
F_2	6.1	5	82%
F_3	6.3	3	90%
F_4	6.1	4	87%
F_5	6.5	4	83%
F_6	6.4	4	82%
F_7	6.4	2	81%
F_8	6.1	3	82%
F_9	5.4	2	75%
F_{10}	5.6	2	76%
F_{11}	5.8	2	80%
F_{12}	5.5	2	76%

Table 2: Kinetic model fitting data for all formulations

Formulationcode	Zero order	First order	Higuchi	Peppas	n
F1	0.93274	0.63266	0.80319	0.87244	0.68729
F2	0.97265	0.69948	0.85115	0.88552	0.63134
F3	0.84276	0.53963	0.73914	0.88851	0.66012
F4	0.91978	0.58552	0.75622	0.83417	0.72947
F5	0.9087	0.59046	0.77377	0.87753	0.69177
F6	0.95806	0.63911	0.79635	0.84741	0.67703
F7	0.84813	0.54889	0.74967	0.89694	0.67189
F8	0.89914	0.58242	0.77029	0.88627	0.68125
F9	0.95093	0.63398	0.79493	0.85079	0.68797
F10	0.97686	0.67641	0.81641	0.84023	0.6406
F11	0.82259	0.53991	0.74022	0.88577	0.64841
F12	0.94192	0.66967	0.84622	0.9221	0.63252

Table 3: Drug deposition data of Emulgels

Formulation Code	% Drug deposited
1	55.6
2	48.86
3	66.66
4	58.4
5	60.12
6	50.12

7	71.5
8	62.2
9	51.6
10	46.32
11	63.8
12	53.06

Table 4: Skin irritation test of Piperine Emulgel on rabbit skin

Rabbit group code	Erythema		Edema	
	1hr	6hr	1hr	6hr
A	0	0	0	0
B	0	0	0	0
C	0	0	0	0

Scores: 0-nill, 1-very low, 2-low, 3-average, 4-severe.

Figure 1: Calibration curve for the estimation of drug Piperine

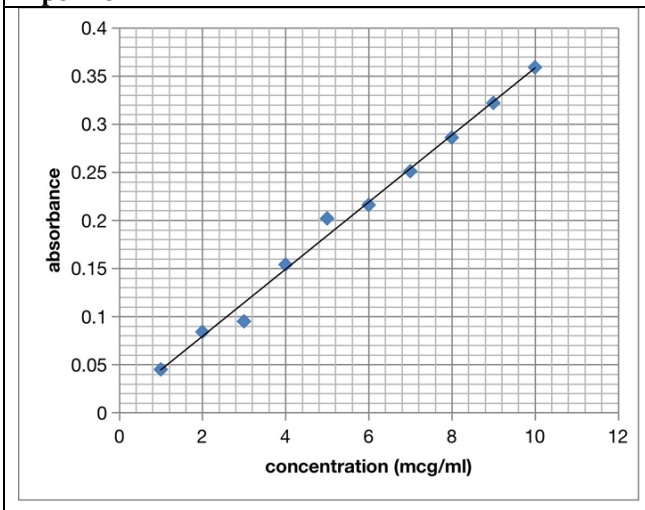


Figure 2: FTIR spectra of drug-Piperine

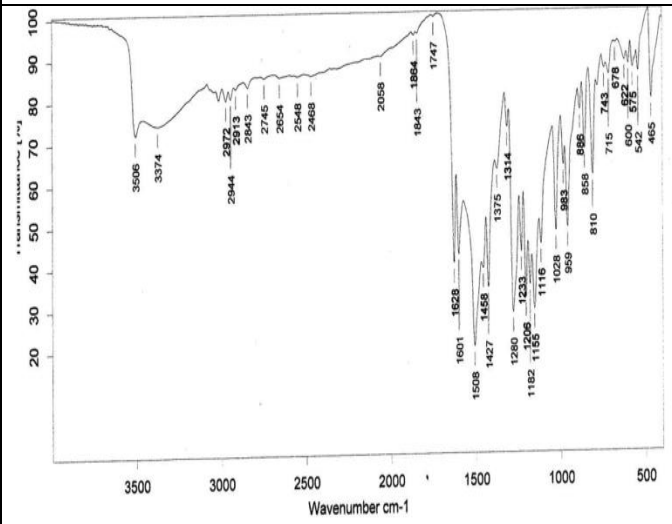


Figure 3: Comparative drug release profiles of emulgels F1, F2, F3,F4

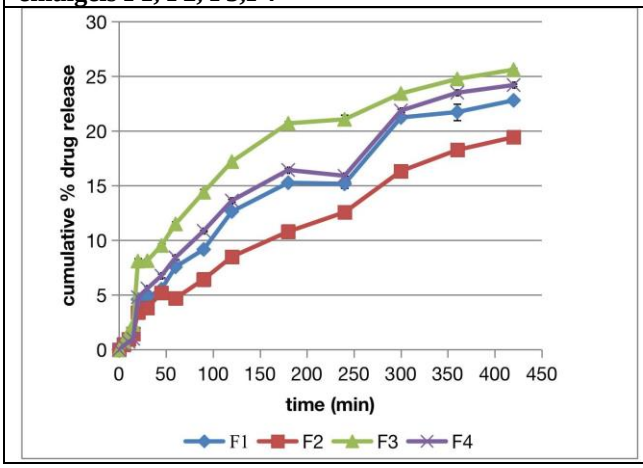


Figure 4: Comparative drug release profiles of emulgels F5, F6, F7,F8

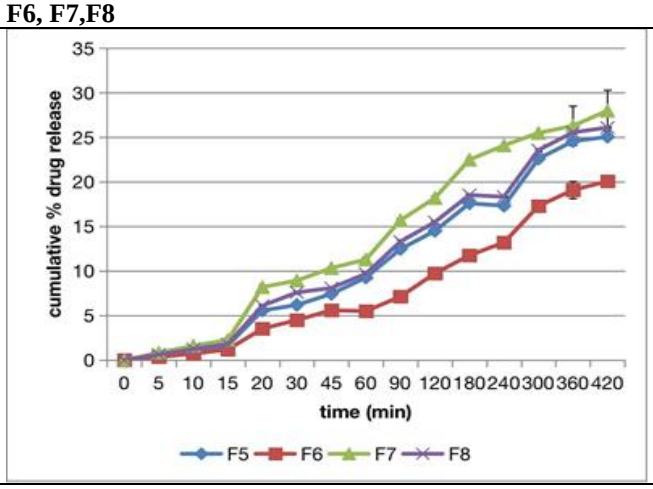
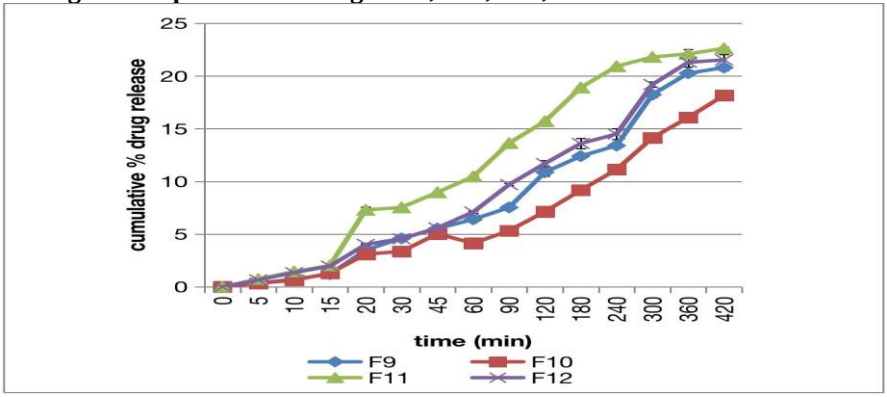


Figure 5: Comparative drug release profiles of emulgels F9, F10, F11,F12



DISCUSSION

FTIR

These peaks of spectrum of pure drug was compared with the peaks of the spectra of physical mixtures. No characteristic changes in the peaks of drug in physical mixture were observed when compared with those of pure drug. No changes in peaks indicates that there are no interactions between the drug and the excipients. So, the excipients are compatible with the drug and can be used for further formulation.

Physical examination

The prepared Piperine emulgel formulations were bright yellowish viscous creamy preparations with a smooth and homogeneous appearance and acceptable biodadhesion.They were also free form gritty particls and greasiness which suggests smooth consistency. But consistency can be optimized only with the help of the consistency tester.

pH study

Generally, normal healthy human skin pH is approxmately around 5.4. If the pH of the formulation is not complying around this range, then pH should be adjusted by using suitable base/acid buffers. The pH values of all the prepared formulations ranged from 5.5 to 6.5. Since, the skin pH is around 5.5, they are considered acceptable as there risk no risk of irritation upon application to the skin and there is no need to alter the pH of the formulation.

Consistency

For topical semisolid formulations, consistency is an important parameter for patient compliance. Possessing good spreadability is also one of the criteria for an emulgel to meet the ideal quantities.

Spreadability

Spreadability is the term expressed to denote the extent of area to which gel readily spread on application to skin or affected part so the therapeutic efficacy of a formulation also depends upon its spreadability which inturn depends upon the consistency. The Consistency and spreadability are interrelated. Lesser the consistency, better the spreadability. Here, the consistency was studied in terms of the time required for the movement of the slide from A to B. For all the formulations, the time was considerably less indicating optimum consistency. So the prepared emulgels were found to have good spreadability indicating better therapeutic efficienty.

Ex vivo diffusion study

The release of the drug from its emulgel formulations can be ranked in the following descending order: F7 > F3> F11 > F8 > F5 > F4> F1>F12 > F9 > F6 > F2 > F10 where the amounts of the drug released after 7 hours were 27.1%, 25.22%, 22.548%, 26.1%, 25.06%, 24.2%, 22.8%, 21.53%, 20.82%, 20.06%, 19.43%, 18.16% respectively. Zero order is the best fit model for the diffusion of all the formulations because it is having the maximum r2 value.

Skin deposition study:

The rank of all the formulations for Skin deposition is as same as the ex vivo diffusion study i.e., F7 > F3 > F8 > F5 > F4 > F1 > F6 > F2> F11 > F9> F12 > F10. And the deposition values are higher values with maximum of 71% whereas diffused drug values are very less indicating that most of the drug is deposited within the layers of the skin. This may be because of the lipophilic nature of the stratum corneum which facilitates the permeation of the drug which is lipophilic in nature into the layers of the skin and hydrophilic nature of the dermis layer which resists the movement of the drug Piperine crossing the skin. This indicates better deposition of the drug within the skin layers which is a desired effect for the drug Piperine for its anti inflammatory action which is a localized and targeted action.

Skin irritation test

The rabbits were checked for redess, swelling, irritation at specific time intervels on the skin of rabbit after the test. There was no edema and erythema observed on the skin of the rabbits indicating all the excipients are compatable with the skin and do not cause any irritation.

CONCLUSION

The topical Piperine emulgels were prepared and evaluated. All the formulations showed acceptable physical properties, pH, consistency, drug diffusion, deposition and no irritation on skin. Ex vivo diffusion values are less whereas skin deposition values are high. The high skin

deposition facilitates the anti inflammatory activity of the drug Piperine. In drug release studies, emulgels were compared with resect to concentrations of oil phase, emulsifier and type of gelling agent. The HPMC-based emulgel with the liquid paraffin in its low level and the emulsifying agent in its high level proved to be the formula of choice, since it showed the highest drug release and drug deposition.

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