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Oral Bioavailability of Curcumin Enhanced Using Different Surfactant for Preparing Proniosomal Gel

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Abstract

Purpose: The aim of the present study was to enhance the oral bioavailability of curcumin using different surfactant and vehicle for preparing proniosomal gel. **Methods:** Curcumin comes under BCS Class IV which is having low solubility and low permeability and poor bioavailability. Buccal drug delivery can bypass such problems and leads to increase in bioavailability. Proniosomes offer excellent potential for improved drug delivery through versatile routes, by overcome the permeation barriers. Trial batches of proniosomal gel are prepared by coacervation phase separation method using different concentration of surfactant (Span 20, Span 40, Span 60, and Span 80) with cholesterol, soyalecithin, and vehicles such as 0.1% glycerol solution or pH 6.8. The formulated systems were characterized to find out the effects of surfactant on vesicle size, % entrapment efficiency, and % drug release and permeation at 6 h. Stability studies for proniosomal gel were carried out for 4 weeks. **Results and Conclusion:** It suggested that formulation (F2) containing Span 20 and phosphate buffer pH 6.8 has high entrapment efficiency, drug release, and permeation as compare to the other formulations and it can enhance the delivery of curcumin through oral route and can improve the bioavailability of drug.

Keywords: Curcumin, Bioavailability, Enhancement, Span 20, Span40, Span 60 and Span 80

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Introduction

The curcumin which is natural origin obtained from turmeric its IUPAC name is curcumin, 1, 7-bis (4-hydroxy-3-methoxyphenyl) -1, 6-heptadiene-3, 5-dione), having small molecular weight, hydrophobic polyphenolic compound, isolated from the rhizomes of *Curcuma longa*, family Zingiberacea.[1] It is mostly found in tropical and subtropical region throughout the worldwide. It is commonly cultivated in Asian countries and it is extensively used in Unani, Sidddha, and Ayurveda system.[2] According to BCS Class IV, curcumin has poor solubility and poor permeability.[3] It has been observed by trials on human and mouse that oral consumption of curcumin has less bioavailability as it undergoes intestinal metabolism. These obstacles can be eliminated by preparing in the form of liposome, noisome, nanoparticle, or using provesicular approach such as proniosomes.[4,5]

Niosomes are closed vesicular bilayer structures developed non-ionic amphiphilic surfactants. They are analog to liposomes, but supersede liposomes about their improved chemical stability, higher penetration property, low production cost, and facile scaling-up and also provide affinity toward target site.[6,7] Due to the physical instability of niosomes, it is developed in the form of proniosomes. Proniosomes are semisolid liquid crystalline product of non-ionic surfactant which is easily formed on dissolving the surfactant in minimum amount of acceptable solvent and the least amount of aqueous phase.[8] On hydration, due to rearrangement of lipids and surfactant in an aqueous medium, proniosomes transform into niosomes. Proniosomes can avoid the limitations of niosomes, for example, aggregation, leakage, fusion and provide convenience in storage, distribution, and transportation.[9] Proniosomal gel in buccal delivery does not require hydration before application. These can be applied as a gel base. The gel base helps in adhesion of the formulation to the buccal mucosa. It can reduce the side effects of drugs and increase therapeutic effectiveness. Proniosomal gel can entrap both hydrophilic and hydrophobic drugs.[10] These are generally transparent, translucent, and yellow semisolid gel texture, which makes them physically stable during storage and transport.[11]

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Experimental

Materials

Curcumin was a gift sample from Amruta Herbals Pvt. Ltd. Soya lecithin and cholesterol were purchased from Hi-Media Laboratories (Mumbai, India). Span 20, 40, 60, and 80 were purchased from Central Drug House (Mumbai, India) and used as received.

Methods

UV spectrophotometric analytical method

Weighed quantity of curcumin was added into methanol AR grade in volumetric flask. Different concentration were prepared up to 20 µg/ml by diluting the stock solution with

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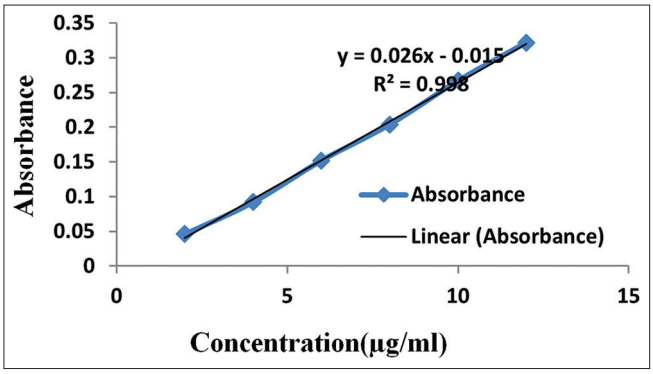

Figure 1: Standard plot of curcumin in phosphate buffer pH 6.8

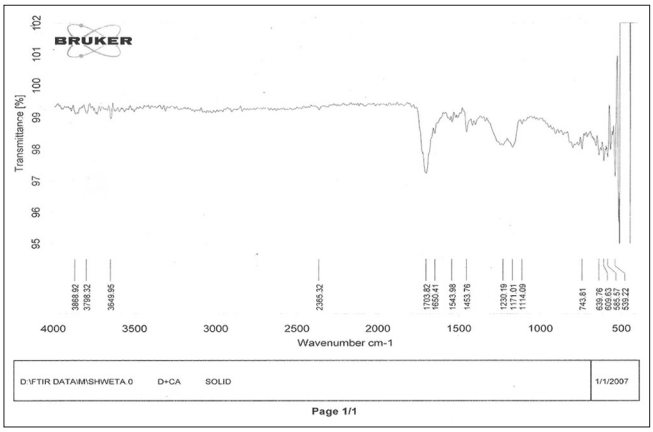

Figure 2: The FTIR shows the compatibility studies of physical mixture. This study was done to check the interaction between drug and excipients

Figure 3: Vesicle size of proniosomal gel

methanol. The absorbance was measured at against methanol as blank. The drug concentrations of curcumin were analyzed by UV-spectrophotometer (Shimazdu, Japan) at 424 nm.[12]

Drug excipients compatibility study

The mixture of drug and excipient in the 1:1 ratio was prepared. The mixture was placed in tightly sealed glass vials and kept it at

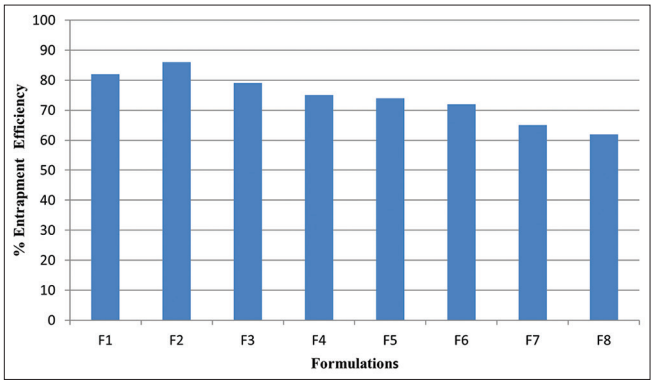

Figure 4: Comparison of % entrapment efficiency of all eight formulations

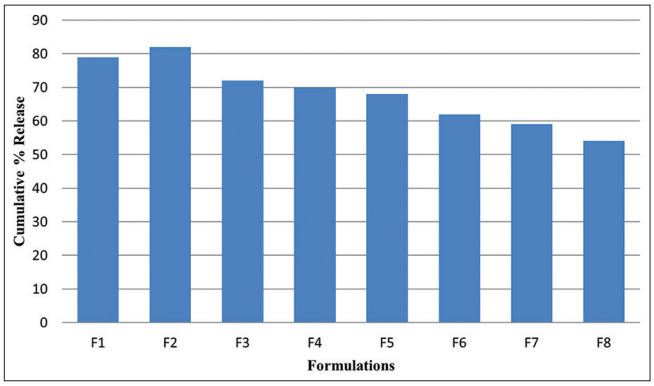

Figure 5: Comparison of cumulative % release of all eight formulations

Figure 6: Ex- vivo permeation study

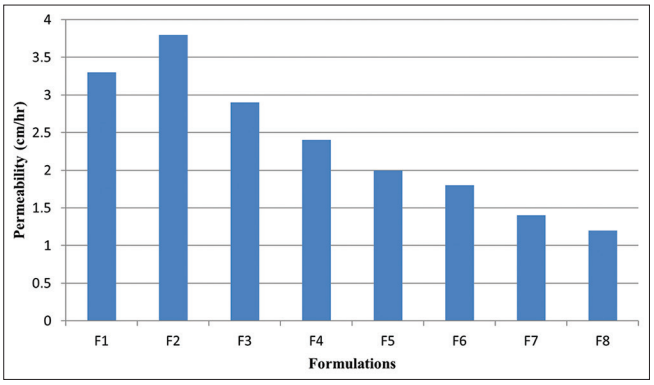

Figure 7: Comparison of permeability of all eight formulations

Table 1 : Trial batches using different surfactant

Batches	*Drug (g)*	*Cholesterol (g)*	*Soya lecithin (g)*	*Span 20 (g)*	*Span 40 (g)*	*Span 60 (g)*	*Span 80 (g)*	*0.1% glycerol solution (ml)*	*Phosphate Buffer pH 6.8 (ml)*	*Ethanol (ml)*
F1	0.1	0.1	0.1	0.8				2.5		2.5
F2	0.1	0.1	0.1	0.8					2.5	2.5
F3	0.1	0.1	0.1		0.8			2.5		2.5
F4	0.1	0.1	0.1		0.8				2.5	2.5
F5	0.1	0.1	0.1			0.8		2.5		2.5
F6	0.1	0.1	0.1			0.8			2.5	2.5
F7	0.1	0.1	0.1				0.8	2.5		2.5
F8	0.1	0.1	0.1				0.8		2.5	2.5

Table 2: Result of entrapment efficiency for selection of surfactant (*n=3, mean±SD)

S. No.	*Batches*	*Entrapment Efficiency (%)*
1.	F1	82.02±0.045
2.	F2	86.74±1.023
3.	F3	79.62±0.821
4.	F4	75.77±2.072
5.	F5	74.54±1.002
6.	F6	72.68±1.064
7.	F7	65.45±3.043
8.	F8	62.05±0.845

Table 3: Result of cumulative % release for selection of surfactant (*n=3, mean±SD)

S. No.	*Batch*	*Cumulative % release*
1.	F1	79.05±0.532
2.	F2	82.12±0.721
3.	F3	72.23±0.035
4.	F4	70.45±0.048
5.	F5	68.21±0.845
6.	F6	62.06±0.066
7.	F7	59.00±1.002
8.	F8	54.06±0.142

Table 4: Result of permeability for selection of surfactant (*n=3, mean±SD)

S. No.	*Batches*	*Permeability (cm/h)*
1.	F1	3.3244±0.066
2.	F2	3.8882±0.004
3.	F3	2.9421±0.282
4.	F4	2.4272±0.312
5.	F5	2.0358±0.762
6.	F6	1.8762±0.072
7.	F7	1.4277±0.292
8.	F8	1.2126±0.525

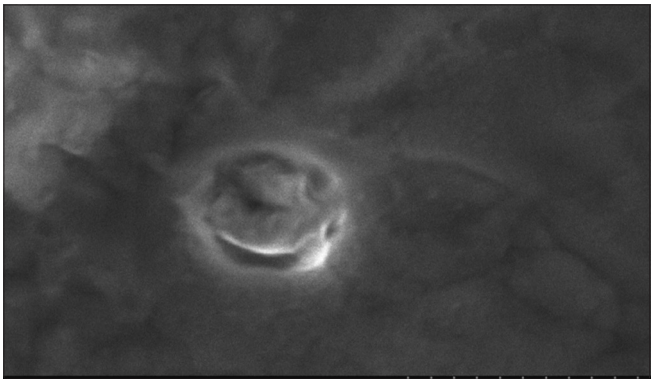

Figure 8: Visualization by scanning electron microscopy

25°C ± 60% RH to 40°C ± 75% RH for 4 weeks to check any caking, discoloration, liquefaction, and odor or gas formation.[13]

FTIR

Infrared spectra of drug with other surfactant were obtained using FTIR spectrophotometer (Bruker, Alpha-T, Lab India) by conventional KBr pellet method. All the powder samples were dried to obtaining any spectra to remove the influence of residual moisture.[14]

Selection of surfactants and solvents

The trials batches from A1-A8 drug loaded proniosomes were prepared by coacervation phase separation method using different concentration of surfactants (Span 20, Span 80, Tween 60, and Tween 80), soyalecithin, cholesterol, 0.1% glycerol solution, or phosphate buffer 6.8 and ethanol as shown in Table 1. Precisely, weighed amount of surfactant, cholesterol, soya lecithin, and drug was placed into a vial with 2.5 ml of ethanol into it. All the ingredients were mixed with a glass rod and vial was closed with a lid to prevent the loss of solvent from it and warmed over water bath at 60–70°C for about 5 min until the surfactants were dissolved completely. Vehicle was then added and the mixture was allowed to cool at room temperature (25°C) until it converted into gel form.[14,15] All the batches were evaluated for entrapment efficiency, drug release, and drug permeate (%).

Vesicle size analysis

The vesicle size of proniosomal gel was evaluated using projection microscope. One gram of each formulation was spread uniformly on glass slide and observed under microscope to study size and shape under 45 X lens.[16]

Percentage Entrapment Efficiency

0.2 g of proniosome were diluted with 10 ml of phosphate buffer 6.8. The aqueous dispersion was ultrasonicated (PRAMA Ultrasonicator) for 10 min and centrifuged (REMI, Model-RM-12CBh) at 20,000 rpm at room temp for 30 min. The supernatant was collected and then analyzed using U.V spectrophotometer for unentrapped drug at 424 nm. The percentage of drug encapsulation was then calculated by the equation: [10]

EE (%) = Total drug-Unentrapped drug/Total drug × 100

In vitro drug release and ex vivo permeation

In vitro drug release studies were performed using Franz diffusion cell. Diffusion cell comprising two compartment, first one is

donor compartment and the receptor compartment containing the receptor solution which is pH 6.8. The capacity of receptor compartment was 15 ml and the area of donor compartment which is exposed to receptor compartment was 1.41 cm^2. The cellophane membrane and oral mice mucosa were mounted between the donor and receptor compartment. The mucosa was dipped in pH 6.8 for 24 h before use. The animal study protocol was reviewed and approved by the Institutional Animal Ethics Committee of Hindu college of pharmacy, 585/02/C/CPCSEA. The receptor compartment was surrounded by a water jacket and heat was provided by hot plate and Teflon coated bead (Bio-craft Scientific Systems Pvt. Ltd., Agra) was used to stir the receptor solution. At aliquot of 5 ml was collected at predetermined time intervals 30 min, 1, 2, 3, 4, 5, and 6 h, respectively, and replaced with equal volume of fresh fluid to maintain constant receptor phase volume. Samples withdrawn were analyzed by spectrophotometer (Shimazdu) at 424 nm.[10,17]

Scanning electron microscopy (SEM)

The surface characteristics of the F2 formulation were studied by SEM.

Stability studies

The stability of prepared Proniosomal gel F2 formulation by keeping the gel at three different temperature (4–8°C), room temperature (25 2 C), and oven (45 2 C) for 1 month.[18]

Results and Discussion

Preparation of Calibration Curve

The graph obeyed beer lamberts law in the selected concentration range as shown in Figure 1. The calibration equation for straight line was observed to be y = 0.028x–0.015 with correlation coefficient as 0.998.

Drug Excipient Compatibility Study

Compatibility study with different excipients at 25°C ± 60% RH and 40°C ± 75 % RH (physical compatibility) and was observed for physical changes (color change, liquefaction, lump formation, and odor). After 2 and 4 weeks, no physical changes were observed in the vials containing drug and excipients. The compatible excipients were selected, namely, Span 20, cholesterol, and soya lecithin.

FTIR Analysis

FTIR spectroscopy was done to check the compatibly between drug and other excipients. The characteristics IR peaks observed for curcumin include C=C (1500 cm^{-1}) and C-O peak (1300 cm^{-1}). The FT-IR spectra of binary mixture of drug with soyalecithin, cholesterol, and Span 20 showed no changes which indicated that there was no interaction between curcumin and other excipients as shown by Figure 2.

Selection of Surfactant and Vehicle

Trial batches of proniosome were formulated to select the suitable surfactant and vehicle. Total eight formulation were prepared which contain different surfactant Span 20, Span 40, Span 60, and Span 80 with different vehicle such as 0.1% glycerol solution and phosphate buffer. Each batch was evaluated for entrapment efficiency, drug release, and permeability for best choice for 6 h.

Vesicle Size

The vesicle size of all formulations ranging from 4.25 to 9.45 μm. The vesicle of all eight formulations is round in shape. In Figure 3 vesicle size of one formulation is shown.

Entrapment Efficiency

The hydrophilic lipophilic balance plays an important role in controlling drug entrapment of the vesicles. The HLB value decreases with increasing the length of alkyl chain, whereas HLB value of 8.6 gives highest entrapment efficiency and entrapment efficiency decreases as the HLB value decreases. Span 20 has HLB value 8.6, Span 40 HLB value is around 6.2, Span 60 HLB value 4.7, and Span 80 HLB value 4.3. The highest entrapment efficiency occurs in a series such as Span 20 >, Span 40 >, Span 60 >, and Span 80 as shown in Table 2 and in Figure 4 a graph ploted between % entrapment efficiency and formulations.[18]

In vitro Drug Release

The drug release from the vesicles was depend on the surfactant. The release of drug from the prepared pronisomal gel from Span 20 was slower formulation containing Span 40 and Span 60 and Span 80 and hence Span 20 shows high percent drug release through the system as compare to other Spans 20. Hence, F2 formulation has better release as comparision to other formulations as shown in Table 3 and in Figure 5 Comparison of Cumulative % release of all eight formulations are shown.[19]

Ex vivo Permeation Study

The gel transition temperature increases resulting in decreased leakage of drugs, but it penetrates slowly. Span 40 and Span 60 have high transition temperature 42 and 56–58°C respectively.[17] They need high temperature to form liquid crystalline state due to which they are less permeable. Span 80 has negative value −12°C, it causes material to liquefy at room temperature, and it cannot form gel at lower concentration of cholesterol.[20] As shown in Table 4, Curcumin was best encapsulated by proniosomal gel prepared using Span 20. Figure 6, showing the ex-vivo permeation study using franz diffusion cell and Figure 7, showing a permeability of different formulations.

SEM

SEM for the optimized formulation (F2-3 μm) was carried out. The results were shown in the following SEM photograph. Figure 8 shows the SEM of F2 formulation.

Stability Studies

The optimized formulation (F2) was found to be stable for period of one month; it can be observed that the gel formulation showed no major alteration in relation to encapsulation efficiency and vesicle size.

Conclusion

The authors concluded that curcumin was successfully prepared using surfactant Span 20 and it will enhance the oral bioavailability of surfactant. The prepared curcumin gel with Span 20 show high entrapment efficiency, smaller particle size, high drug release, and permeation as compared to other formulations prepared with Span 40, Span 60, and Span 80.

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