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DESIGN AND IN-VITRO EVALUATION OF PENTAZOCINE HYDROCHLORIDE MICROEMULSION TRANSDERMAL GELS

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Abstract:

The purpose of this study was to design and in-vitro evaluation of Pentazocine hydrochloride microemulsion transdermal gels.. Results: The mean particle size of the microemulsion gel formulation was found to be 126.6 ± 0.1 nm and The PDI was found to be in the range of 0.341 ± 0.6.. The mean zeta potential value of the microemulsion gel was found to be -26.1 ± 0.3 mV. Transmission electron micro-graphs of the optimized formulation, revealed that the globules of the developed microemulsions are spherical and discrete and have uniform droplet size distribution. The in vitro permeation was found to be 92.2 ± 0.5% and 76.4 ±0.1% in 24 hours for microemulsion gel and plain gel respectively

Key words Microemulsion, particle size & Transmission electron micro-graphs.

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INTRODUCTION:

Transdermal drug delivery systems (TDDS) are defined as complete or independent, discrete dosage forms which, when applied to the intact skin, deliver a predetermined amount of drug, through the skin, at a controlled rate to the systemic circulation. These systems are considered to be among the best types of controlled drug delivery systems1-4.

The concept of a microemulsion was first introduced in the 1940s by Hoar and Schulman to describe transparent single-phase systems that are generated by titrating a milky emulsion with hexanol17. Since their first description, microemulsions have been extensively studied as delivery systems, due to their multiple advantages. Microemulsions are clear, optically isotropic and thermodynamically stable systems generally composed of a blend of oil, water and surfactant(s)18. Microemulsions are advanced dosage forms in the emulsions field. Microemulsions are clear/transulennt and thermodynamically stable dosage forms. The globule size varies in the region of 100 to 200 nm19-21. There are differences between microemulsions and emulsions. Nanoemulsions and microemulsions are described similarly: they are both low- viscosity dispersions with an internal droplet size smaller than 200–250 nm . However, nanoemulsions are kinetically, not thermodynamically, stable. Nanoemulsions present the advantage of being formed with smaller amounts of surfactants, but the preparation of stable nanoemulsions generally requires expensive, high-energy input methods[5-9].

MATERIALS AND METHODS:

Materials

Pentazocine hydrochloride was received from Sai Lifesciences, Pune, Other chemicals used were of analytical grade.

Methods

From the screening results of pseudo-ternary phase diagrams the five ratios yielded clear and stable microemulsions but the ratios which showed broad microemulsion regions were found to be 2:1 and 3:1 and therefore both the systems were optimized and selected for further studies. According to the results obtained, it is attributed that an increase of the weight ratio or concentration of (surfactant) labrasol resulted in expansion of the ME region2. Further, labrasol causes reduction of the interfacial tension, increasing the fluidity of the interface, thereby increasing the entropy of the system. The microemulsion region is also based on co surfactant along with single chain length surfactant could result in lowering the interfacial tension[10-12].

Initially, accurately weighed amount of pure drug was dissolved in oil phase then the surfactant and the co-surfactant were added to the drug-oil mixture and the whole system was stirred by magnetic stirrer at 400 rpm, at suitable room temperature, until complete uniform distribution of drug in the surfactant and co-surfactant mixture. The whole mixture was titrated with sufficient double distilled water, drop by drop with gentle shaking. At a certain end point, spontaneously a clear, transparent and stable monophasic microemulsion was formed.

In vitro dissolution:

The in vitro drug release studies were performed using vertical Franz diffusion cells with an effective diffusional area of 4.52 cm2 with a capacity of 28 mL. A volume of microemulsion that was equivalent to 5 mg of drug was placed in the donor compartment. Twenty eight millilitres (28mL) of phosphate buffer of pH 7.4 was used as receptor medium to ensure sink condition. The receptor compartment was maintained at 32°C±0.5ºC and was stirred by a magnetic stirrer at 100 rpm. The donor compartment was separated from the receptor compartment by cellulose dialyzing membrane (Membra–Cel MD 34-14, cut-off 14KD), which was soaked overnight in the receptor medium. At pre-determined time intervals (1, 2, 4, 6, 8, 10, 12, and 24 hours), one mL aliquots were withdrawn from the sampling port and were replaced with an equal volume of fresh buffer to maintain a constant volume. The samples were analyzed spectrophotometrically at 272 nm[13-16].

Globule size and Polydispersity Index (PDI)

Globule size and size distribution are the most important parameters for a microemulsion The PDI determination was done with a Zetasizer (Nano ZS, Malvern Instruments, Westborough, MA, USA) at 633 nm. The polydispersity index was calculated by

PDI = X90-X10/X50

Zeta potential

The microemulsions were diluted (1:100) using distilled water and were taken in a cuvette. The cuvette was placed inside the sample holder of a zetasizer (Malvern Nano ZS90, Malvern, UK) for measurement of size. The principle of photon correlation spectroscopy was used for determining the hydrodynamic diameter of the vesicle via Brownian motion. The observations of vesicle size were recorded at 90° light scattering angle and at 25°C. The zeta potential was measured based on the electrophoretic mobility of vesicle which used the Helmholtz–Smoluchowski equation.

Transmission electron microscopy (TEM)

The morphology of the microemulsion formulation was examined by Transmission electron microscopy (TEM-FEI, TECNAI T20, USA) study. One drop of a diluted sample (1 ml microemulsion in 9 ml distilled water) was stained by 2% phosphotungstic acid (PTA) and placed on film-coated copper grids followed by drying at 25◦C before examination under the TEM. The formulation was diluted 1500 times with the dispersion medium i.e. with distilled water at 60º C, to investigate the percolation in the microemulsion[17-19].

RESULTS & DISCUSSION:

Table 1: Physicochemical properties of (2:1 S/CoS) of PTHCL microemulsion

Batch	Particle size (nm)	PDI	Zeta Potential (mV)	*In vitro* drug release
ME1	224±1.5	0.212±0.4	-6.4±0.8	64.1± 0.1
ME2	176.1±0.2	0.416±0.6	-13.4±1.2	71.2±0.6
ME3	148.2±0.4	0.187±0.1	-19.1±0.9	92.6±1.2
ME4	161.3±1.1	0.254±0.6	-11.2±1.1	82.8±1.8
ME5	210.1±1.5	0.232±0.5	-9.1±0.7	78.4±1.4
ME6	251.1±1.3	0.464±0.7	-5.4±1.2	62.4±1.6
ME7	278.6±0.8	0.312±0.2	-4.6±1.2	56.2±1.1
ME8	331.4±1.2	0.364±0.5	-5.2±1.6	51.8±1.5
ME9	354.1±1.1	0.241±0.7	-3.1±1.4	46.2±1.6

Table 2: Physicochemical properties of (3:1 S/CoS) of PTHCL microemulsion

Batch	Particle size (nm)	PDI	Zeta Potential (mV)	*In vitro* drug release
ME1	306.1±1.5	0.612±0.4	-12.1±0.8	64.12± 0.1
ME2	278.2±0.2	0.316±0.6	-14.6±1.2	76.23±0.6
ME3	234.6±0.4	0.288±0.1	-19.4±0.9	79.16±1.2
ME4	186.2±1.1	0.154±0.6	-21.1±1.1	86.12±1.8
ME5	112.6±1.5	0.132±0.5	-28.4±0.7	98.42±1.4
ME6	161.4±1.3	0.164±0.7	-24.6±1.2	92.41±1.6
ME7	254.2±0.8	0.212±0.2	-16.4±1.2	78.21±1.1
ME8	334.4±1.2	0.264±0.5	-13.3±1.6	61.28±1.5
ME9	361.6±1.1	0.541±0.7	-9.1±1.4	56.24±1.6

Particle size and size distribution (nm)

The mean globule size of the microemulsions was found to be in the range of 148.2 ± 0.4 nm to 354.1 ± 1.1 nm and the PDI was found to be in the range of 0.187 ± 0.1 to 0.464 ± 0.7 for 2:1 ratio of microemulsion. The microemulsions prepared in the 3:1 ratio show the globule size in the range of 112.6 ± 1.5 nm to 361.6 ± 1.1 nm and the PDI in the range of 0.132 ± 0.5 to 0.612 ± 0.4. The results showed that the small globule size of microemulsion was due to the high concentration of surfactant and co- surfactant in the microemulsion system. The decrease in the globule size can be attributed to the solubilisation of internal phase within a larger number of surfactant micelles, which are consequently swollen to a lesser extent1. The content of the surfactants mixture in microemulsion significantly enhanced the transport of drug through skin. Moreover, the small globule size of the microemulsion droplets

also affects the percutaneous absorption of the drug. So a similar trend in analysis of globule size with increase in concentration of surfactant was observed in the 3:1 ratio of microemulsion. The higher the PDI lower the uniformity of globule size in the formulation.

Zeta potential

The zeta potential of 2:1 ratio of microemulsion was found to be in the range of -4.6 ± 1.2 mV to -19.1 ± 0.9 mV. The 3:1 ratio of microemulsion shows within the -9.1 ± 1.4 mV to -28.4 ± 0.7 mV. The smaller size microemulsion shows higher zeta potential whereas the larger globule size microemulsion shows low zeta potential. Microemulsions with low droplet size are usually more stable compared with microemulsions with larger droplet size because larger droplets are more susceptible to aggregation or coalescence3. Microemulsions showed net negative charge and addition of surfactants, further contributed negatively to the system. This may be attributed to the fact that the increase in surfactant level resulted in a decrease in surface tension and surface free energy of the formed micelles. The microemulsions were expected to have good physical stability, due to the very small droplet size of the microemulsion there is a large reduction in the gravitational force and Brownian motion which may be sufficient for overcoming the effect of gravity. In addition, smaller droplet size also prevents flocculation. Weak flocculation (cases where the net attractive forces are relatively weak) is prevented, thus enabling the system to remain dispersed with no separation4. Accordingly in the 3:1 ratio of microemulsion shows better stability as it is near to the specified range of zeta potential value and gives an indication of potential stability of the microemulsion, hence this formulation is optimized and further studies were conducted.

		Mean (mV)	Area (%)	Width (mV)
Zeta Potential (mV): -28.1	**Peak 1:**	-28.1	100.0	8.00
Zeta Deviation (mV): 8.00	**Peak 2:**	0.00	0.0	0.00
Conductivity (mS/cm): 0.266	**Peak 3:**	0.00	0.0	0.00
Result quality :Good				

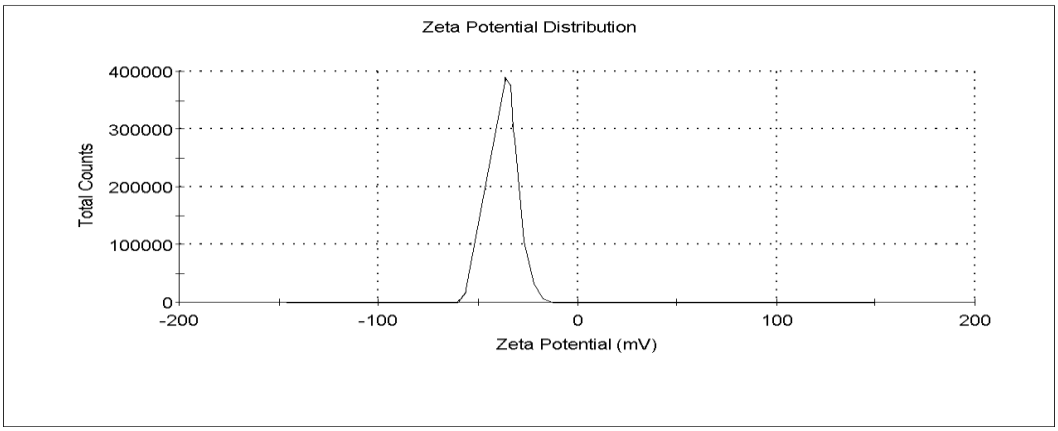

Figure 1: Zeta potential (mV) graph showing (3:1) S/CoS ratio of ME 5 microemulsion

		Mean (mV)	Area (%)	Width (mV)
Zeta Potential (mV): -19.1	**Peak 1:**	-19.1	100.0	7.34
Zeta Deviation (mV): 7.34	**Peak 2:**	0.00	0.0	0.00
Conductivity (mS/cm): 0.263	**Peak 3:**	0.00	0.0	0.00
Result quality :Good				

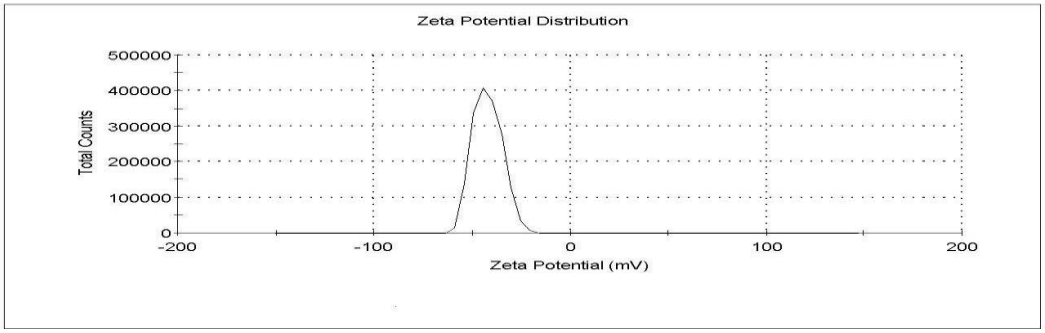

Figure 2: Zeta potential (mV) graph showing (2:1) S/CoS ratio of ME 3 microemulsion

In vitro drug release of microemulsion

The drug release testing is a fundamental part of drug product development, and manufacture. It is also employed as a quality control tool to monitor batch-to-batch consistency of the drug release from the microemulsion systems. The in vitro drug release from the (3:1 ratio) formulations (ME1 to ME9) was found to be slow, gradual and spread over 24 hours. Cumulative percent drug release values rose steadily upto 12 hours and then the rise in release tapered off. After 24 hours there was no further rise in the values of cumulative percent drug release. The in vitro percent drug release from the 2:1 ratio of microemulsion was found to be in the range of 46.2 ± 0.5% to 92.6 ± 0.2%, whereas the release from the 3:1 ratio of microemulsion was found to be in the range of 52.1 ± 0.2% to 98.42 ± 0.1%. The highest drug release values were found to be 92.6 ±0.2% and 98.42 ± 0.1% for 2:1 ratio of ME3 and 3:1 ratio of ME5 for 24 hrs respectively. The microemulsion drug release mechanism is influenced by composition of the microemulsion system. The 3:1 ratio of microemulsion showed a higher drug release when compared to the 2:1 ratio of microemulsion. It was observed that in vitro drug release followed the percent encapsulation efficiency of the microemulsion. The formulations with 3:1 ratio of the systems showed lower particle size and higher surface area. This large surface area of the microemulsion help to accommodate PTHCL into smaller nanoglobules. Of the 2:1 and 3:1 ratios of microemulsions, ME3 and ME5 batch released 92.3% and 98.8% respectively. This might be due to the lower particle size and higher percentage of encapsulation efficiency.

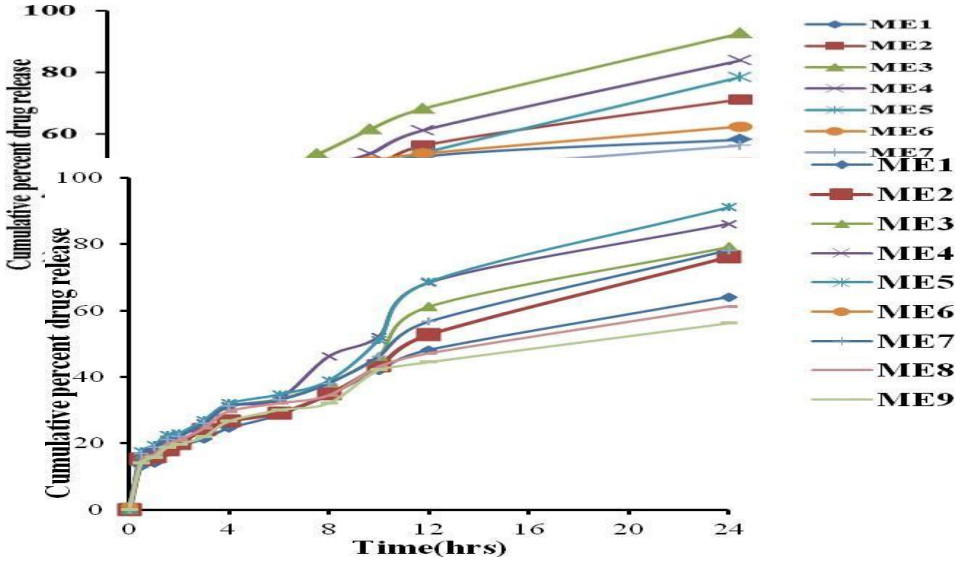

Figure 3: In vitro cumulative percentage drug release profiles of PTHCL microemulsion (2:1 S/CoS ratio)

Figure 4: In vitro cumulative percentage drug release profiles of PTHCL microemulsion (3:1 S/CoS ratio)

Transmission electron microscope

Transmission electron microscopy revealed nearly uniform desired globule size with round and slight elliptical shape. There was absence of coalescence after 100 times dilution which suggests the physical and thermodynamic stability6. It is seen that oil globules are spherical in shape and have smooth surface. There is no aggregation of droplets seen and globule size was found to be 100 nm size range.

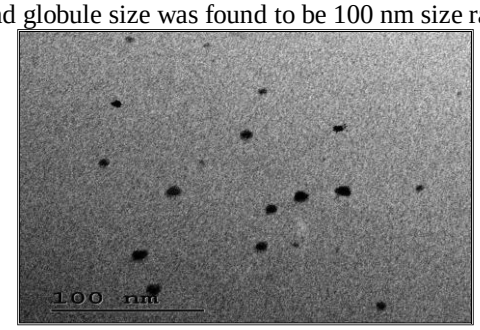

Figure 4.5: Transmission electron micrographs of the optimized PTHCL loaded microemuls

CONCLUSION:

The present study was carried out with an aim to study the potential of microemulsion based gel as a carrier for transdermal delivery of the chosen drug, PTHCL. The zeta potential value of the microemulsion gel formulation was found to be -26.1 ± 0.3 mV. Zeta potential values influence the shelf stability of the gels and can effect the pharmaocokinetic properties of the gel system. Particle aggregation is decreased for charged particles with zeta potential due to electric repulsion. The microemulsion based gel could significantly increase the accumulative uptake of PTHCL in skin as compared to plain gel. It also had no significant effect on the microscopic structure of the rat skin. Thus, microemulsion based gel demonstrated advantage over plain gel formulation in improving the skin tolerability of PTHCL indicating its potential in improving patient compliance and transdermal delivery.

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Conflict of Interest

The authors declare no conflict of interest, financial or otherwise.

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