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Release Engineered Microemulsion based Carvedilol gel for Transdermal Drug Delivery

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ABSTRACT: Background: Carvedilol (CAR) is the most widely prescribed drug for long-term treatment of hypertension. The transdermal route offers many advantages over the oral dosage form, such as improving patient compliance, bypassing first-pass metabolism, sustaining drug delivery and making it possible to terminate treatment when necessary. **Aim:** The aim of the present study was to develop microemulsion gel of optimized microemulsion formulation for transdermal delivery of Carvedilol with objective to increase bioavailability and plasma half-life, leading of drug. **Method:** The microemulsion was prepared by the spontaneous emulsification method. The pseudoternary phase diagrams were constructed to obtain the microemulsion. The microemulsion gels were evaluated for drug content, pH, viscosity, stability, *in vitro* drug release. The drug release profile of optimized and marketed formulation was compared. **Result:** The optimized W6 batch was found to be having 51.52 %v/v of surfactant and co-surfactant combination. Acrypol TR 2 (1.0 %w/v) exhibited better characteristics compared to other gelling agents. **Discussion:** It has been seen from the drug release data that nearly 70 % drug has been released in 24 h in optimized formulation. The optimized formulation gives better drug release (71.21 %) than marketed (66.11 %). The drug content, viscosity and pH of the drug were found excellent. **Conclusion:** On the basis of *in vitro* drug release, drug content and stability study, it could be concluded that Microemulsion based Gel (MBG) dispersed system is suitable for Topical administration as well as for sustained delivery in order to enhanced bioavailability.

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Key words: Carvedilol, Microemulsion, *in vitro*, Transdermal Drug Delivery, Surfactant, Gel.

INTRODUCTIONS:

Carvedilol (CAR) is the most widely prescribed drug for long-term treatment of hypertension. CAR is rapidly absorbed from the gastrointestinal tract (80 %), but the oral bioavailability remains low because of significant first-pass hepatic metabolism [1]. Long-term treatment of hypertension by CAR via oral administration may result in poor patient compliance because of low bioavailability and short plasma half-life, leading to

increased frequency of administration. So an alternate route of administration is needed [2]. The transdermal route offers many advantages over the oral dosage form, such as improving patient compliance, bypassing first-pass metabolism, sustaining drug delivery and making it possible to terminate treatment when necessary[4]. CAR possesses ideal physicochemical characteristics to be formulated as a transdermal patch. But CAR belongs to BCS class Π drug so it requires increase in solubility.

Microemulsions (ME) are thermodynamically stable, transparent, low viscosity and isotropic dispersions of oil and water stabilized by an interfacial film of surfactant molecules, typically in conjunction with co surfactants which is a short chain length amphiphile, possessing limited water solubility. Microemulsions contain huge oil/water interfacial areas and very low interfacial tension. Microemulsions are thermodynamically stable which means that they form spontaneously when the components are brought together and stay stable as long as the ingredients are intact. Its oil and water domains are much smaller, which means light can pass through without much scattering and so microemulsions are clear or translucent. microemulsions are dynamic systems with structures, which may or may not be droplets that form, disintegrate and reform in milliseconds [4-6].

In addition, there are distinct differences in their method of preparation, since emulsions require a large input of energy while microemulsion does not. The latter point has obvious implications when considering the relative cost of commercial production of the two types of system [7-9].

MATERIALS AND METHODS:

Materials:

CAR was obtained as a gift sample from Troikaa Pharmaceuticals Ltd, Ahmadabad. Acrypol TR 2 and Acrypol 940 were obtained as a gift sample from Corel Pharma, Ahmedabad. Other materials used in the study (Isopropyl myristate (IPM), PEG 400, n-butanol, tween 80, sodium carboxymethyl cellulose, sodium hydroxide and potassium dihydrogen phosphate) were of analytical grade. Double-distilled water was used throughout the study.

Preparation of Microemulsion of CAR:

The ME of CAR was prepared using IPM as oily phase (2 %), n-buatanol and PEG 400 (1: 2) in combination as a co-surfactant (3.5 %) and tween 80 as a surfactant (5 %). Water (2 %), tween 80 and IPM were sequentially mixed and subsequently titrated with cosurfactant till the solution gets transparent. The amount of tween 80, IPM and water was optimized by preparing various batches as mentioned in Table 1. A pseudo ternary phase diagram was constructed using TRIPLOT to help in optimization of ME. The best formulation was utilized to develop a microemulsion based gel (MBG).

Characterization:

Drug content:

About 1 gm microemulsion based gel (MBG) were kept into a 100 ml buffer (pH 7.4), and shaked continuously for 24 h and filtered. In filtrate solution, the drug content was determined using UV-VIS spectrophotometer at a wavelength of 224 nm.

Measurement of pH:

The pH of carvedilol microemulsion formulations was determined by using digital pH meter. The measurement of pH of each formulation was done in triplicate and average values were calculated.

Viscosity:

The measurement of viscosity of the prepared microemulsion was done with a Brookfield Viscometer DV II (LVDL-II+PX) at 25 ±0.3 °C.

***In vitro drug release study*:**

In vitro drug release studies were performed using a Franz diffusion cell with a receptor compartment capacity of 25 ml. The optimized MBG formulation was placed over the cellophane membrane. The receptor compartment of the diffusion cell was filled with phosphate buffer pH 7.4 having 25 % PEG 400.

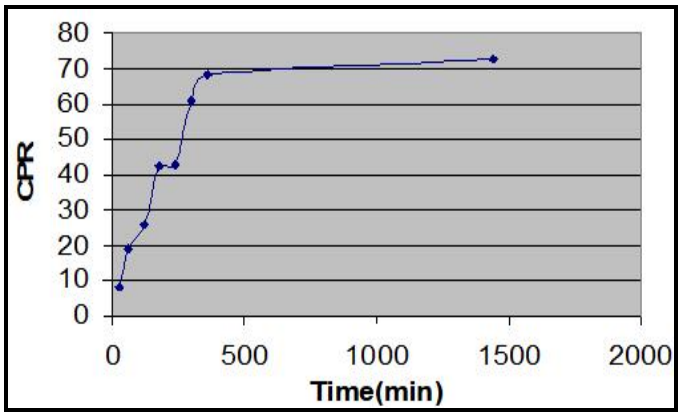

Fig 1. *In vitro* drug release profile of optimized (F6) formulation.

The samples were withdrawn at different time intervals and analyzed for drug content using UV-VIS spectrophotometer at a wavelength of 224 nm. The

cumulative amounts of drug released were plotted against time [10].

Stability study:

Stability studies of the Microemulsion samples were carried out by subjecting them to temperature stability and centrifugation. The temperature stability study was carried out by keeping the Microemulsion sample at temperatures (2 - 8°C and at room temperature) for two months and visual as well as particle size measurements inspection was carried out by drawing samples at monthly intervals for the subsequent months [10-12].

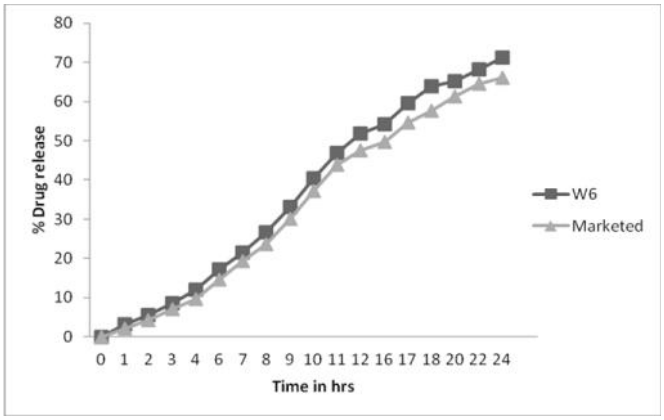

Fig 2. Comparative % drug release between optimized and marketed Gel formulations.

RESULTS AND DISCUSSIONS:

The spontaneous emulsification method was found to be efficient method for successful formulation of microemulsion. The optimized batch of microemulsion gel drug content was found to be 88.36 ±1.47 %, which reflected it possessed satisfactory drug content. The viscosity of microemulsion gel was found to be 124 × 10^5 cps. This value as interrelated with literature revealed that this viscosity value is the significant factor for maintaining stability of microemulsion in gel form. The pH of the formulation was 7.6, which is more or less resembles to neutral pH, demonstrating that the formulation shall be nonirritant to skin.

The optimized formulation was selected from the ME region on the basis of minimum proportion of surfactant and co-surfactant combination. The optimized W6 batch was found to be having 51.52%v/v of surfactant and co-surfactant combination. Acrypol TR 2 (1.0 %w/v) exhibited better characteristics compared to other gelling agents. It has been seen from the cumulative percentage release v/s time graph that nearly 70 % drug has been released in 24 h. By the comparison between marketed and optimized formulation as given in Fig 2, shows that optimized formulation gives better drug release (71.21 %) than marketed (66.11 %). As per the results no evidence of phase separation or any flocculation or precipitation was observed in some Microemulsion formulation. The few of formulation show no sign of phase separation when subjected to centrifugation at 10000 rpm for 30 min. Thus, it was concluded that the few of Microemulsion formulation was stable thermally as well as under stressful conditions.

CONCLUSION:

On the basis of *in vitro* drug release, drug content and stability study, it could be concluded that Microemulsion based Gel (MBG) dispersed system containing 51.52 %v/v of surfactant and co-surfactant combination. Acrypol TR 2 (1.0 %w/v) exhibited better characteristics compared to other gelling agents, thus it is suitable for Topical administration as well as for sustained delivery in order to enhanced bioavailability.

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