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Original Article

FORMULATION OF MICROEMULSION BASED GEL OF SALBUTAMOL SULPHATE AND IT'S *IN VITRO* STUDIES

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ABSTRACT

Objective: The aim of this study was to develop a microemulsion based gel system considering transdermal delivery of Salbutamol with a purpose to increase the solubility and membrane drug deliverance.

Methods: Oleic acid was favored for oil phase owing to the proficiency of solubility in this study. Despite surfactant and co-surfactant was determined by virtue of their solubilizing strength wherewith they developed MEs. Accomplishing Franz diffusion cells equipped with cellulose membrane for *in vitro* study. The Polymer carbopol 934 were used for based gel preparation to enhance the viscosity of microemulsion for transdermal utilization. The advanced micro emulsion-based gel, which was assessed for pH, centrifugation, spreadability conductivity, drug content, viscosity, SEM, XRD and stability studies.

Results: The process of drug escape from microemulsion gel-based was noticed to pursue Korsmeyer-peppas model kinetics. The designed, microemulsion gel-based displayed acceptable stability layer than 3 mo. Drug release microemulsion within 24 h was observed 74%.

Conclusion: The results illustrate that deliberated effort to establish microemulsion based gel (F3) was likely to produce sustained action of drug release (78.3%) and be permitted auspicious vehicle for transdermal distribution of Salbutamol.

Keywords: Salbutamol, Oleic acid, Cellulose membrane, SEM

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INTRODUCTION

In the past, people used to place solid material under the skin and oral dosage form to treat different pathological conditions but with the passage of time technological accomplishments have reduced the hurdles which were faced by the oral drug delivery system such as a first-pass effect,side effects and non-compliance of patients. And first transdermal preparation of patch integrated with scopolamine was developed and approved by the United States in 1979 to treat motion sickness [1]. Salbutamol is a drug that belongs to the selector's β-adrenergic agonist class and act as a bronchodilator to treat many diseases such as chronic obstructive pulmonary disease, bronchitis and asthma. Oral delivery of Salbutamol is infrequent, as this drug holds bioavailability of 50% by absorbing from the gastrointestinal tract and metabolism by liver. Thus intranasal delivery crops up an interesting alternative [2]. To improve physicochemical characteristics of the parent drug, any acidic or basic drug could be converted into salt. Likewise, salbutamol shows ion pair with ulphate [3]. Skin is major organ of the body which carries multiple layers. Transdermal route utilizes one or more than one layers of skin to produce therapeutic effects locally and systemically [4]. Microemulsion is one of transdermal preparation comprises of thermodynamically stable W/O or O/W mixture composed by water, oil, surfactant and co-surfactant along size range of 10-100 nm of the droplet. When microemulsion is assimilated with gel, it gives rise to emulgel possessing the qualities of both dosage forms with good bioavailability [5]. The motives of this research work are to formulate microemulsion based gel of salbutamol sulphate and to study its *in vitro* ex-vivo characteristics.

MATERIALS AND METHODS

Chemicals

Salbutamol, Tween 20 and Tween 80 span 85, Glacial acetic acid Menthol and PLGA, Mineral oil, Cyclohexane, Ammonium acetate, Carbopol, Mineral oil, Ethanol, Propyl paraben, Potassium dihydrogen phosphate, Acetone, Oleic acid, Palmito stearyl, Acetonitrile, n-hexane isopropyl alcohol, Sodium hydroxide pellets, Triethylamine and Propylene glycol.

Instruments

Digital weighing balance (Sartorious), Whatman Filter Paper, Oven (Binder US PATS), pH Meter (Jenway 3510), Optical Microscope(LeicaDM2500), UV-Spectrophotometer double beam (Shimadzu 1601), Conductometer (Jenwa, Water deionizer, Vacuum pump (Stuart RE3022C), Automatic Dissolution apparatus USP, Vortex mixer, Programmable rheometer, Centrifuge tubes, Centrifuge machine(Appendrof), Disposable syringes, Electric balance, Franz diffusion cell, Tewameter SEM, Syringe filter unit, Peristaltic pump, Water distillation apparatus (AUTOSTIU Freshman-4), Ultra low temperature freeze, Sonicator and Cellulose acetate membrane filters.

Salbutamol sulphate calibration curve

To establish a salbutamol sulphate standard curve, a solution in stock was come about in 10 mg of salbutamol sulphate powder, dissolved in distilled water (50 ml) through the stirring of multiple minutes and accomplishing 100 ml volume in addition to phosphate buffer contains (pH 7.4). From the stock solution, dilutions were made as 0.312, 0.625, 1.25, 2.5, 5, 10 and 20 µg/ml. At 242 nm, ultraviolet (UV)-visible spectrophotometer (Shimadzu UV-1601, Japan) was employed and absorbance of entire dilutions were analyzed. The graph for linearity is delineated in fig. 1

Formulation of microemulsion

The microemulsion was developed through approaching the procedure of Gul et al. [6, 7]. Manually a mixture of a surfactant (polysorbate 20) and Co surfactant (ethanol) in 2:1 ratio. 4.6 g sample of surfactant was added in 0.5 g of oleic acid (oil) and assimilated with the magnetic stirrer. Surfactant mixture and Sabutamol Sulphate (0.5 g), are added to oleic acid (oil) and mixed strenuously up to dissolve totally. Being skin penetration enhancer, 0.2 g of dimethylsulfoxide was put together in the microemulsion. Finally, under continuous stirring (1200 rpm) 4.4 g distilled water was gradually added on room temperature.

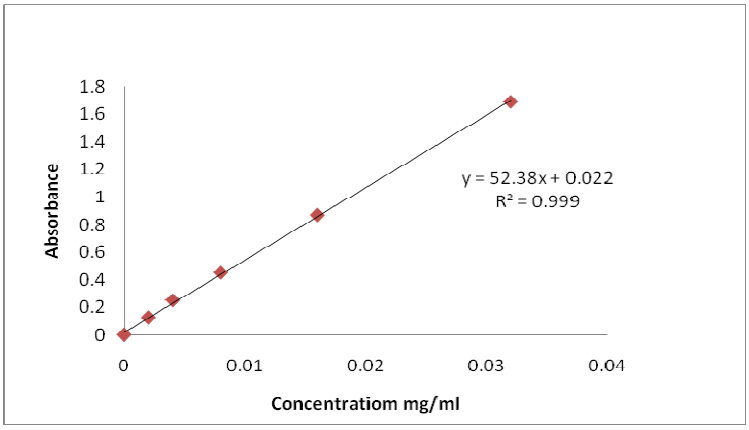


Fig. 1: Calibration curve of salbutamol sulphate

Formulation of based gel

A carbpol gel was developed by gently dissolving 1g of carbopol in 17g of distilled water slowly by the application of magnetic stirrer in as much as 2 h at room temperature. Till the formation of gel, keep adding trimethylamine to achieve the pH 4-7 [7, 8].

Formulation of microemulsion based gel of salbutamol sulfate

For the formulation of microemulsion gel-based, 82g of microemulsion containing salbutamol would be vigorously mixed with 18g of carbopol 934 gel base at various rpm and room temperature for 10, 15 and 20 min respectively, and 100g polymer-based gel containing salbutamol sulphate is achieved by the same method Five formulations were prepared.

Physicochemical determination

Evaluation of microemulsion based gel

Viscosity

Brookfield RVDV ultra, programmable Rheometer (Brookfield Engineering Laboratories Middleboro, MA) with spindle CP41 was taken to measure viscosity of several formulations in triplicate by rotating the spindle at different speeds at 25°C. The readings were taken as triplicate and average of readings was acclaimed [9-11].

Consistency

By dropping cone technique, the pseudoephedrine gel consistency was estimated. This technique incorporates a cone, joined in holding, dropped rod in the position of equal distance from edges of a gel-filled cup with far off 10-cm space in the center. After 50 seconds, the distance lead up in the inner gel cup was perceived to regulate the consistency [12, 13].

Homogeneity

By visual observation, the sample containing pseudoephedrine gel was analyzed for its homogeneity. To examine any lumps, transparent slender glass tubes profused with gel and seen below the light [13].

Spreadability

In label of diameter, spreadability of all formulations was calculated by weighed quantities of formulations by depositing on microscopic slide (10g) then sandwiched it on another microscopic slide (10g). Then diameter was measured by consolidation between two slides and production of circle of the formulation was produced. All formulations were evaluated for spreadability by establishing the spread of a 0.5 g formulation after two 10-g microscopic slides were contrasted [13-15].

Conductivity measurement

To commit the conductivities of blank micro emulsion and drug loaded microemulsion and drug loaded microemulsion based gel Conductometer WTW cond 1971 (weithein, Germany) was utilized at 25 °C in triplicate [6]

pH measurement

pH meter (WTW ino lab, Germany) was controlled at 25°C in order to obtain blank pH values of microemulsion, drug-loaded microemulsion, unfilled microemulsion based gel and drug filled microemulsion based gel [10, 16]. The values through pH measurements of the salbutamol gels were calibrated [10].

Centrifugation

To determine phase separation test, 5g of formulation was taken in centrifuge tubes held in centrifuge machine and rotated for 30 min at 3000 rpm. After particular time phase separation of formulation, tubes were analyzed at 25 °C [6, 7].

Drug content

To calculate salbutamol sulphate amount in processed gel, a 10-mg sample of individual wastaken. Then mixed by the application of stirring in HCl solvent (100-mL) and filtered by using 0.2-µm membrane filters. Then analyzed using a calibrated UV-visible spectrophotometer. The salbutamol sulphate percentage was determined [7, 9, 16].

***In vitro* study protocol**

For *in vitro* study of salbutamol formulation across the synthetic membrane, Franz diffusion cell apparatus (Perme Gear, USA) was promoted. In this procedure, in donor and receptor jacket of franz cell apparatus, synthetic cellulose membrane was securely positioned. As receptor medium phosphate buffer and ethyl alcohol (75:25) was taken and 12 ml was carried in the receptor compartment. For upper donor compartment, 1g of microemulsion based gel was carried and filled in it. In receptor, medium temperature was ensured at 37 °C throughout the study. At 0.5, 1, 2, 3, 4, 5, 6, 12, and 24 h of intervals 1 ml of sample was carried from receptor medium and each sample was restored with a medium which was fresh but also have same particular temperature. Restored sample was examined at 242 nm by UV Spectrophotometer [7, 17]. To confirm slight differences in the six Franz cells, further experiments were carried in triplicate.

***In vitro* release kinetic studies of salbutamol microemulsion based gel**

Through spectroscopy technique, the impregnate quantity of drug was identified and calculated. At that instant, when drug amount (mg) in the receptor medium (sample) was taken and observed (0-24 h). The linearity regression study and release criterion of the drug impregnation for every formula were evaluated. To determine the release of drug and impregnation of a drug by membrane, correlation coefficient (r) was valued by calculations just to show the case of drug release and impregnation is a zero order, first order,

Higuchi, Korsmeyer-Peppas, or follows Hixon-Crowell diffusion release model. This is done for each formula. Entire calculations were executed with respect to the subsequent kinetics equations accomplishing a validated software program, DDSolver for Microsoft Excel 2007 [8].

Model equation

- Zero order Qt = Qo+Kot
- First order In Qt = lnQo+K1t
- Higuchi Qt = K H√t
- Korsmeyer-Peppas plot Mt/M∞ = Ktn
- Hixon-Crowell Qt/Qo=Kktn

Scanning electron microscope (SEM)

Hitachi S4000N was taken for Scanning Electron Microscope, at vacuum in the vicinity of various pressures and liquid samples of thin films were prepared and then dried at 105°C and put to imaging for further evaluation [18].

X-ray diffraction

For unfilled microemulsion, microemulsion based gel, active drug and drug loaded microemulsion based gel, the crystallinity of salbutamol sulphate was determined by using X-Ray diffractometer (Bruker D8 Discover Germany) contains Ni filtered CuK alpha radiation originate over a range of 8°-60° diffraction angle (2θ) range [17].

Stability studies

Under several storage conditions, the stability of the salbutamol sulphate formulations was analyzed. During the period of three (3) months of storage at 0±1 °C (freezer), 8±0.1 °C (refrigerator), 25±0.1 °C (incubator) and 40±0.1 °C (incubator) samples were examined. Entire formulations were assessed along with diversity in appearance, homogeneity, consistency and pH [6, 11].

Statistical analysis

All kinetic results of statistical analyses were completed on DD Solver (Microsoft Excel 2007) [6, 11, 14]. For ANOVA calculations SPSS (version 18.0, IBM, USA) was employed [6]. To calculate the flux (J) as µg/h/cm 2, each formulation data were adjusted to the kinetic model.

RESULTS AND DISCUSSION

The pH, homogeneity, spreadability, drug content of salbutamol sulphate formulation and Consistency were identified (table 1). Formulations were equivalent in an aspect of their, liquefaction, phase separation, color and further parameters were satisfying pH likewise. The formulations exhibited pH in between (5.5 and 6.5) compatible to pH examined in previous Studies of formulations of salbutamol sulphate microemulsion based gel topically with respect to normal human skin pH range (4.5 to 6.5) [8, 13]. Spread ability and consistency were examined during a period of 90 d. With slight shearing pressure spreadability divergent from 4.6 to 5.7 g/cm/s. Homogeneity was ensured with the absence of lumps. Drug content of salbutamol sulphate was in span of 97.10–99.31% and microemulsion based gel has shown good existence of Uniformity. Total physical evaluated parameters suggest convenient results for transdermal application. By performing stability studies for 3 mo (90 d) at 25±1 °C and 40±1 °C results achieved were satisfying and ensured that microemulsion based gel is good enough at (25±1 °C) as % age of drug leftover is not reduced by more than 10 % [6]. At the end of 3 mo, it is also clearly seen from results of standard deviation that at 40 °C standard deviation is slightly greater and it was aside from normal and appropriate ranges whereas 25±1 °C standard deviation was smallest and it fell into sufficient range. So it arrived at the judgment that at 25±1 °C formulations predicts the standards required for preparation of microemulsion based gel, which is the matter of interest in extent stability studies. In this study, (0.025-µm cellulose membrane) was taken which was 180 µm thick statistically it was observed that the membranes has good released. The formulation (F3) showed the maximum released (78.30%). This study is compatible with earlier works of Gul *et al.* [6]. Who gave a detailed account in words about discharge of caffeine from water in oil emulsion and alcoholic gels. The data of each formulation was fit to the first pass permeation model as shown in table 2. Discharge of Salbutamol sulfate from the transdermal formulation, and its release through membrane of cellulose, are delineated in fig. 2. Obtained results pointed out that (69.10-78.30%) drug amount, discharged through each formulation of microemulsion based gel after 34 h of the study was restored in the receptor solvent present in the cellulose membrane.

Table 1: Physical parameters values for salbutamol based gel and salbutamol based gel formulations

Salbutamol based gel formulation	pH	Spreadability (g. cm/s)	Homogeneity	Drug content (%)
F1	5.5	4.6	Good	97.10
F2	5.9	4.8	Good	98.09
F3	6.4	4.9	Good	99.31
F4	5.8	5.1	Good	98.10
F5	6.4	5.2	Good	98.28

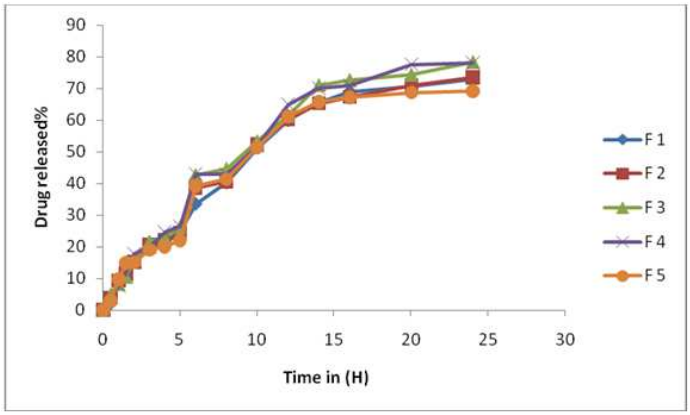


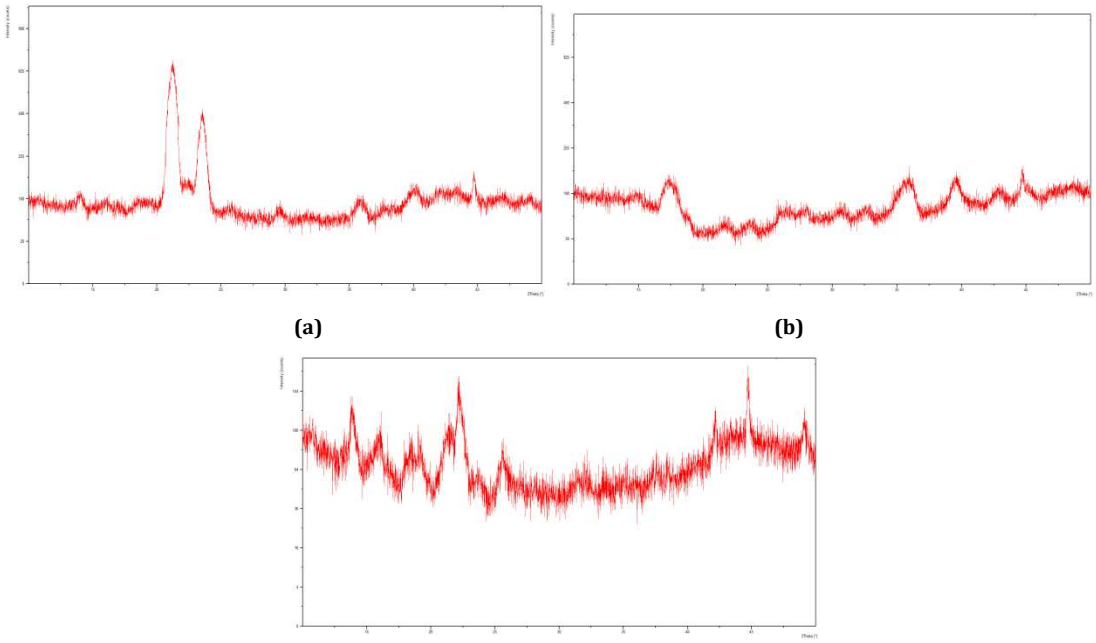
Fig. 2: Release of salbutamol ME gel 1% (W/V) via cellulose membrane

Table 2: Salbutamol release from the formulations by using cellulose-based membrane

(R^2) is the coefficient correlation						
Formulation type	**Zero(0) order**	**First(1st) order**	**Higuchi**	**Hixon-crowell**	**Korsmeyerpeppass**	**Best-fitting model**
F1	0.8587	0.9823	0.9383	0.9680	0.9669	First order
F2	0.8482	0.9824	0.9429	0.9654	0.9676	First order
F3	0.8505	0.9853	0.9402	0.9725	0.9639	First order
F4	08537	0.9852	0.9402	0.9735	0.9402	First order
F5	0.8587	0.9823	0.9383	0.9680	0.9383	First order

XRD studies

X-ray diffraction studies were applied to endorse chemical and physical properties of salbutamol and polymeric matrix of Gel Pure B showed fine peaks of diffraction at the value of 13.52°, 18.23°, and 21.18° etc at an angle of 2θ. X-ray diffractograms are positioned in (fig. 3, a) that show crystalline nature of salbutamol, while fig. 3, b shows no peak i. e of blank ME, which was also reported previously by sami *et al.* [17]. In fig. 3 (c) Salbutamol and Carbopol, displayed peaks having minor intensity, while fused peaks were displayed in diffractograms of the salbutamol gel. Irregular peaks of salbutamol demonstrated that drug changed in to an amorphous type in ME based gel with a molecularly discrete nature.



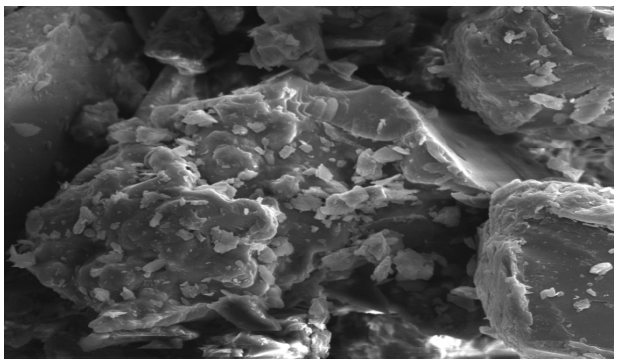
(a) **(b)**

(C)

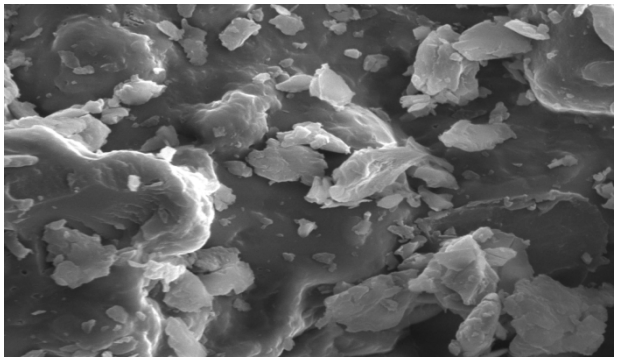
Fig. 3: X-ray diffractograms of salbutamol drug (a), blank microemulsion (b) and salbutamol ME based gel formulation(c)

SEM

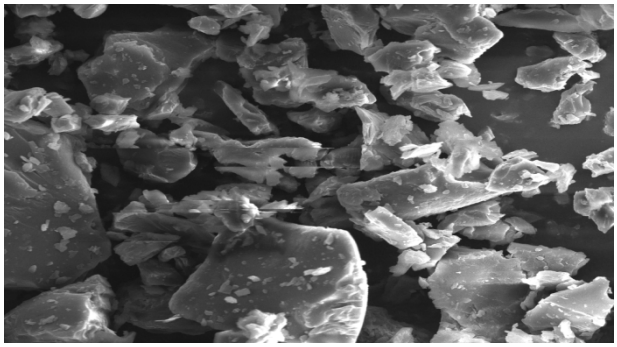
The surface morphology of the drug was studied under an electron microscope. Gapes having irregular shapes was observed under electron microscope because the polymer used was water-soluble in nature. SEM results showed in fig. 4 that the drug used in gel, ME and ME based gel was almost the same and not affected in formulations.



(a)



(b)



(c)

Fig. 4: Displays polymeric gel-based surface morphology only (a), different magnification powers exhibits surface morphology of ME and ME based gel (b, c)

CONCLUSION

In this study, novel microemulsion based gel formulations as transdermal delivery was developed. Salbutamol sulphate as a component of Micro emulsion-based gel has a good affinity for the membranes and enhancement of drug released in the cellulose membrane. The statistical data showed the formulations were physicochemically stable. An *in vitro* release studies significantly showed that the optimized formulations data together promote the suggestion that microemulsion based gel formulations showed potential novel delivery systems to improve the release and stability of salbutamol.

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Nil

AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

We have no conflict of interest.

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