ORIGINAL ARTICLE

INTERNATIONAL JOURNAL OF EXPERIMENTAL AND BIOMEDICAL RESEARCH

Published by Pharma Springs Publication Journal Home Page: https://pharmasprings.com/ijebr

Formulation and Evaluation of Transdermal Delivery of Salmeterol Via Ethosomes

Sravani M*[1], Pradeep Kumar M[1], Satrasala Neelima[2]

[1]Department of Pharmaceutics, Vasavi institute of pharmaceutical sciences, Vasavi Nagar, Peddapalli (Village), Sidhout (Mandal), YSR Kadapa (Dist)-516247, Andhra Pradesh, India
[2]Department of Pharmacology, Vasavi institute of pharmaceutical sciences, Vasavi Nagar, Peddapalli (Village), Sidhout (Mandal), YSR Kadapa (Dist)-516247, Andhra Pradesh, India

Article History:

Received on: 25 Jul 2022
Revised on: 14 Aug 2022
Accepted on: 16 Aug 2022

Keywords:

Transdermal Delivery,
Salmeterol,
Ethosomes,
Liposomes

ABSTRACT

The present study consists of a Salmeterol drug carried out for maximum solubility in aqueous buffers for the Formulation and Evaluation of Transdermal Delivery of Salmeterol Via Ethosomes. These studies are critical to confirm the drug structure, activity, degradation rate, and release pattern with various polymeric substances used in the formulation. An investigation of such prepared formulations through Leica optical microscope and SEM revealed a dominancy like spherical-shaped vesicles. Laser diffraction research indicates significantly different shapes among liposomes and ethosomes (P G .05). The entrapment percentage of 49.7% was at 40% (vol/vol) ethanol. The recognized specific liposomes were much more steady as more significant ethanol concentrations. Based on previous outcomes, liposomal equation five has been chosen for further in vitro drug permeability and rodents' epidermis discharge research. This comparison to ethosomal formulations containing 20% and 30%, but also 40% ethanol (formulas 6, 7, and 8, respectively). The speed and quantity of set to release opioids is a balancing act among two factors: Opioid affinity of about cysts and solubility of the drug through fatty acid of a stratum corneum. Statistical analysis of previous findings (i.e., the proportion like Stratum corneum penetrated via rodents epidermis now since 24 hrs. A method like the secretion kinetic model has been analyzed through likely to fit permeability statistics towards the zero-order, first-order, but also Higuchi diffusion designs.

*Corresponding Author

Name: Sravani M
Phone: +91 7989112957
Email: sravanimedamreddy@gmail.com

eISSN: 2583-5254 pISSN:

DOI: https://doi.org/10.26452/ijebr.v1i3.388

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INTRODUCTION

Transdermal delivery allows localized treatment of superficial tissue and systemic therapeutic since topical application towards the epidermis [1]. Nevertheless, one such delivery route has many difficulties, even as the epidermis behaves as just a physical barrier against permeation like chemotherapeutic drugs. A wide range of topical preparations has indeed developed for treating local medical situations [2]. The first transdermal system, such as systemic delivering a three-day patch and providing scopolamine to treat morning sickness, was authorized in the US in 1979 [3]. Presently, there seem to be transdermal drug delivery processes for certain substances just as estradiol, fentanyl, lidocaine as well as testosterone; combined effect patches usually contains a couple of opioid such as contraceptive methods as well as hormone treatments; but also iontophoretic as well as ultra-

sonic delivery [4]. The transdermal path to distribute water-soluble opioids, a transdermal drug delivery like polypeptide but also macromolecules, DNA, and small-interfering RNA, had also posed particular problems [5]. Ethosomes have been non-invasive delivery carriers and permit opioids to succeed in deep layers of skin or even the circulatory system. Ethosomes have been established, such as transdermal drug delivery of such an opioid [6].

MATERIALS AND METHODS

Salmeterol collected from PARC, Chennai. Phosphatidylcholine, Cholesterol, and Diacetyl phosphate were found in Merck Pvt. Ltd. All abundant chemicals and chemical agents utilized in this study are of analytical grade.

Methodology

FTIR Study

Drug polymer compatibility studies have been conducted through FTIR (Fourier transform infrared spectroscopy) to affirm that such entrapment like opioids inside the polymeric system design involves just the physical phenomenon, and no interplay remains in place as for opioids but also polymer combined effect. FT-IR spectra of pure opioids, all polymeric materials used, and the combined impact like an opioid, but polymeric materials have been begun to substantiate identification of an opioid and recognize an interplay of an opioid only with emigrants [7].

Its compatibility of it with the opioid within a composition has been affirmed through FT-IR spectral analysis. FT-IR spectra like salmeterol and formulation containing all polymers were determined using the Shimadzu FT-IR 8300 spectrophotometrically by potassium bromide pellet method in the wavelength region of 4,000 to 400 cm^{-1}. A methodology comprised of dissipating one specimen through potassium bromide and compacting it into the discs by implementing a pressure of five metric tons for five minutes in such a hydraulically operated. A pellet has been positioned through the light path, and the spectra have been acquired [8].

Formulation of Liposomes

Liposomes have been able to prepare even by evaporation of the solvent method. Exactly 50 mg of phosphatidyl through the soybean lecithin, Cholesterol, and dicetylphosphate have been disintegrated in a small quantity like diethyl ethanol: chloroform (1:1.5) mixture inside a round-bottom flask. An aqueous phase, usually containing Salmeterol (15 mg), has been added towards the organic solvent whereby the organic-to-aqueous-phase proportion has been 5:1. A weird mix was also sonicated, such as ten min. A steady pale emulsion was created wherein the water, and organic phase strange mix were gradually evaporated there at 55ºC utilizing a rotating vacuum evaporator until a thin film was formed upon the wall of a bottle. An arising film was kept under a vacuum of about removing a trace amount like an organic phase [Table 1]. Such a film was then moisturized with an appropriate amount about an aqueous phase but also abandoned there at 55ºC in a thermostatic managed water bath for 1 hour. A lipid-based suspension has been left standing about as room temp as 1 hour after ultrasonication for 20 minutes [9].

Formulation of Ethosomes

Ethosomes have been able to prepare to go, following a method described earlier. However, the general results from the film have been hydrated with such a hydroalcoholic composition (20%-40% [vol/vol] ethanol) [10].

Evaluation of Ethosomes

Vesicle Morphology

Visual representation through optical microscopy imaging techniques: specimens able to prepare blisters seem to be sufficiently solubilized for high salinity and analyzed using an optical microscope [11].

Vesicle Size Distribution

Statistics have been supplied through into SPSS statistics program (SPSS Inc, Release 14.0 for Windows, Chicago, IL) trying to apply a 1-way variance analysis (ANOVA) experiment to the most minor mean square distinction (LSD) various comparisons [12]. A vesicular shape for every liposomal suspended, but each ethosomal suspension was resolute, through triplicate, through laser diffraction about 25-C (Malvern Mastersizer-S, Malvern Instruments, Manchester, UK). Such as shape measurement techniques, preparedness has consequently improved for ethanol-water (30% vol/vol, ethanol) solutes such as ethosomes and pure water such as liposomes. A polydispersity index (PI) has been resolute like a quantify like homogeneity. The lowest value PI (G0.1) implies a racially homogenous community, whereas PI values 9 0.3 imply diverse characteristics.

Determination of Entrapment Efficiency

An unlimited (unentrapped) Salmeterol content was resolute within the supernatant UV spectrophotometer (Shimadzu UV–1601 PC Double Beam, Kyoto, Japan) there as λmax 216 nm. Proportion vesicular arrangements have been retained overnight at about 4^{o}C and ultra-centrifuged for

Table 1: Composition of Various Liposomes (1-5), Ethosomes (6-8) Solutions

Batches	Phosphatidylcholine (mg)	Cholesterol (mg)	Dicetylphosphate (mg)	Ethanol (% vol/vol)	Salmeterol (mg)
F1	50	10	-	-	15
F2	50	30	-	-	15
F3	50	20	2.5	-	15
F4	50	25	5	-	15
F5	50	25	7.5	-	15
F6	50	25	5	20	15
F7	50	25	5	30	-
F8	50	25	5	40	-

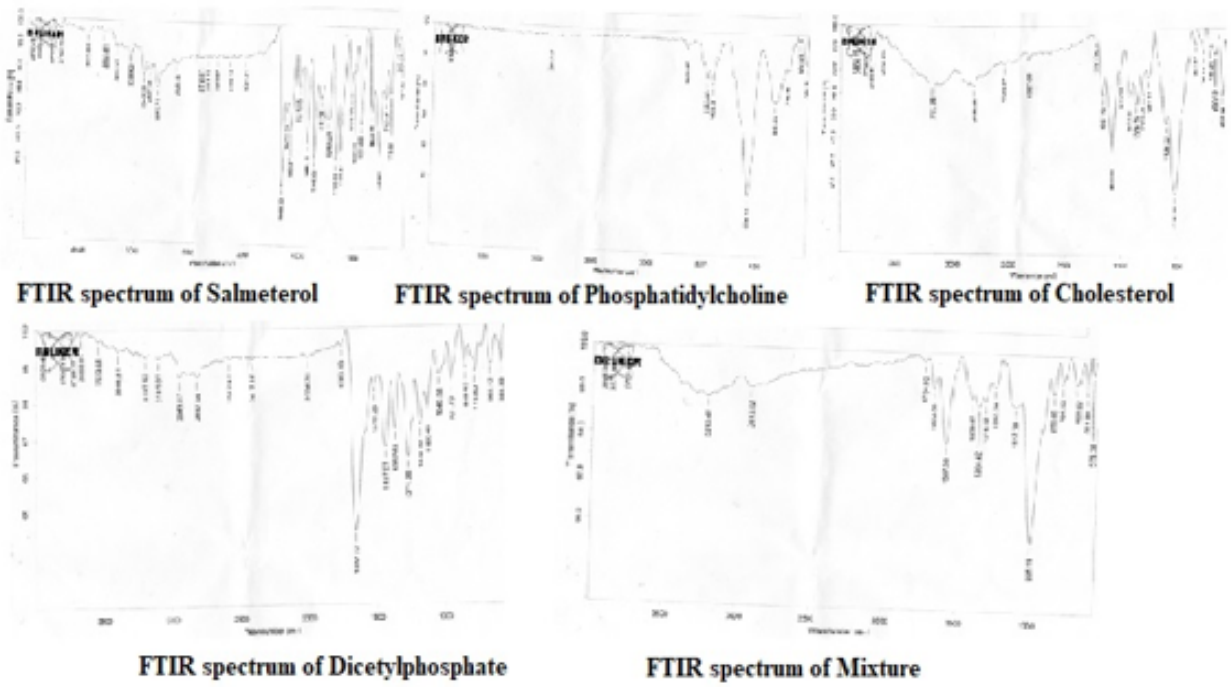

Figure 1: FTIR spectrum of Drug, Excipients, and Mixture

two-hour shifts at about 15,000 rpm [13]. A SS entrapment percentage has been determined using the following formula.

$$EE\ \tfrac{1}{4}\ \tfrac{1}{2}\langle Qt\ -\ Qs\rangle\ \div\ Qt]\times\ 100$$

In Vitro Permeation Studies

Experimental studies have been operating through Franz diffusion cellular, having an effective permeability region of 4.90 cm^2. A temp has been retained at about 37°C ± 0.5°C [14]. A receptor storage area consisted of 20 mL of phosphate-buffered saline (pH 7.4) and was agitated consistently by magnetic stirring at about 50 revolutions per minute [14].

Mathematical modeling for drug release profile

Zero-order kinetics

It describes the system in which the drug release rate is independent of its concentration [15].

$$Q_{ts}\ =\ Q_0 + K_0 t$$

To study the release kinetics, data from *in vitro* drug release studies were plotted as the cumulative amount of drug released vs. Time.

First Order Kinetics

It describes the drug release from the systems where the release rate is concentration-dependent [16].

$$Log\ Q_t\ =\ Log\ Q_0\ +\ K_1 t/2.303$$

The data obtained are plotted as a cumulative log percentage of drug remaining vs. time.

Higuchi Model

It describes the fraction of drug release from a matrix as proportional to the square root of time

Table 2: Interpretation of FTIR Spectral Data

IR Absorption Bands (cm-1)		Bond	Functional Group
Observed Peak	Characteristic Peak		
		Salmeterol	
2927	3300-2500 3000-2850	O-H stretch C-H stretch	Carboxylic acids Alkanes
1670	1760-1665 1710-1665 1680-1640	C=O stretch C=O stretch -C=C- stretch	Carbonyl (general) β-unsaturated aldehydes, ketones alkenes
1483, 1423	1550-1475 1500-1400	N-O asymmetric stretch C-C stretch	Nitro compounds aromatics
1094	1320-1000 1250-1020	C-O stretch C-N stretch	Alcohols, carboxylic acids, esters, ethers Aliphatic amines
		Phosphatidylcholine	
2816,2549,3183	3300-2500 2830-2695	O-H stretch H-C=O: C-H stretch	Carboxylic acids Aldehydes
1737,1667	1760-1665 1760-1690 1750-1735 1740-1720 1710-1665 1680-1640	C=O stretch C=O stretch C=O stretch C=O stretch C=O stretch -C=C-stretch	Carbonyls Carboxylic acids Esters, saturated aliphatic Aldehydes, saturated aliphatic a,β- unsaturated Aldehydes, ketones alkenes
1582	1650-1580	N-H bend	1^0 amines
1517	1550-1475	N-O asymmetric stretch	Nitro compounds
1433	1500-1400	C-C stretch	Aromatics
1368	1370-1350	C-H rock	Alkanes

Continued on next page

Table 2 continued

IR Absorption Bands (cm-1)		Bond	Functional Group
Observed Peak	Characteristic Peak		
		Cholesterol	
3396	3500-3200 3400-3250	O-H stretch N-H stretch	H-bonded alcohols, phenols 10, 20 amines, amides
2943, 2817,2582,3101, 3197,3396	3300-2500 3000-2850 2830-2695	O-H stretch C-H stretch H-C=O: C-H stretch	Carboxylic acids Alkanes Aldehydes
1437	1500-1400	C-C stretch(in the ring)	Aromatics
		Dicetylphosphate	
1367	1370-1350	C-H rock	Alkanes
1587	1650-1580 1600-1585	N-H bend C-C stretch (in the ring)	1^0 amines Aromatics
1409	1500-1400	C-C stretch (in the ring)	Aromatics
		Mixtures	
1364	1370-1350	C-H rock	Alkanes
1587	1650-1580 1600-1585	N-H bend C-C stretch (in the ring)	1^0 amines Aromatics
1409	1500-1400	C-C stretch (in the ring)	Aromatics
1364	1370-1350	C-H rock	Alkanes

[14].

$$Mt/M\alpha = K_H t^{1/2}$$

The data obtained were plotted as cumulative percentage drug release vs. square root of time.

Korsmeyer-Peppas Model (Power Law)

The powerful law describes that the fractional amount of drug release is exponentially related to the release time and adequately describes the release of drugs from slabs, cylinders, and spheres [17].

$$Mt/M\alpha = Kt^n$$

$$Log\,[Mt/M\alpha] = Log\,K + n\ \log\ t$$

RESULTS AND DISCUSSION

Drug Polymer Compatibility

These studies are critical to confirm the drug structure, activity, degradation rate, and release pattern with various polymeric substances used in the formulation. The present study showed no significant shifts in its prominent peaks. So this indicates that there were no compatibility issues of Salmeterol with Phosphatidylcholine, Cholesterol, and Dicetylphosphate. FTIR spectra are shown in Figure 1, and interpreted values are shown in Table 2.

Vesicle Morphology

An investigation of such prepared formulations through a Leica optical microscope and SEM revealed a dominancy like spherical-shaped cysts [Figure 2]. A vesicular is standardized through size as well as seems like a multi-layer.

Vesicle Size Distribution

Laser diffraction research indicates significantly different shapes among liposomes and ethosomes (P G .05). As represented in Table 3, the diameter of varied liposomes medium ranges from 382.3 to 736.6 nanometers, while for ethosomal system design. A tiny PI virtue with most preparations might imply their homogeneity. The shortest virtue (0.11) has been recognized with ethosomal preparations seven and 8, to between. However, a PI valuation like equation 6 (0.24) might imply that now it is heterogeneous distribution.

One deduced that all this expanded reduction within mean vesicular diameters is because of the real presence of acid within vesicles.

This recommended specific ethanol causes a modification of the net charge of a system but also affords this some degree like steric normalization which may surely lead to a lessen within the mean vesicular shape. All such outcomes conform with the results of these other authors.

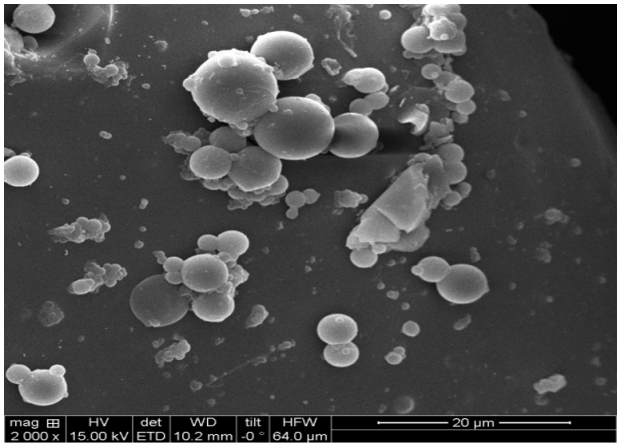

Figure 2: Optical Micrographs of Salmeterol

Entrapment Efficiency

The maximum entrapment percentage of 49.7% was reached at 40% (vol/vol) ethanol. This was recognized as specific liposomes were much more steady as more significant ethanol concentrations. Several factors govern the steadiness and therefore the encapsulation efficiency of vesicles. The first one is the ethanol concentration; a membrane containing greater ethanol concentrations has a smaller membrane structure comparable to forming such a stage as for interpenetrating hydrocarbon chains [Table 3]. Such as, diacetyl phosphate and butanol could exhibit one is trying to stabilize impact within the composition, trying to prevent either at smallest going to delay a formation like coarse vesicular aggregate because of repulsive electromagnetic forces. A second factor has been the existence of lipids, which either appears to contribute to vesicular stability, which provides a greater solidity to a single lipid layer but also enhances the scheme a better stabilization, one lowered likeliness like vesicular fusion, or a better resistance towards the high rotational power exercised through ultracentrifugation.

In Vitro Permeation and Skin Deposition Studies

Of prepared ethosomal preparations, the very best opioid flux ($22.83 \pm 0.56\ \mu$g/cm2/h). Based on previous outcomes, liposomal equation five has been chosen for further in vitro drug permeability and rodents' epidermis discharge research. This comparison to ethosomal formulations containing 20% and 30%, but also 40% ethanol (formulas 6, 7, and 8, respectively). Similar findings might be acquired from such analysis of an opioid flux of all the same methodologies towards the recipient storage area, seen in Table 5. Opioid flux virtues like ethosomal methods 6, 7, and 8 have been significantly

Table 3: Physical Characteristics of the Vesicles: Diameter, Polydispersity Index, and Entrapment Efficiency Percentage (Mean ± SD, n = 3)

Batches	Vesicle Diameter (nm)	PI	Entrapment Efficiency (%)
F1	736.6 ± 34.5	0.29 ± 0.05	38.6 ± 2.1
F2	659.3 ± 41.7	0.35 ± 0.08	41.1 ± 1.6
F3	573.7 ± 32.7	0.32 ± 0.04	46.8 ± 2.2
F4	522.3 ± 33.6	0.28 ± 0.04	48.6 ± 2.2
F5	476.4 ± 35.5	0.41 ± 0.07	41.2 ± 4.1
F6	442.9 ± 38.1	0.24 ± 0.07	45.8 ± 5.2
F7	382.3 ± 36.4	0.22 ± 0.04	48.9 ± 4.3
F8	378.9 ± 17.4	0.11 ± 0.05	49.7 ± 4.8

Table 4: Drug Flux Values of the Different Formulas inthe Receiver Solution via Mice Skin (Mean ± SD, n = 3)

Batches	Drug Flux (μg/cm2/h)
F5	9.51 ± 0.44
F7	22.83 ± 0.56
F8	15.53 ± 0.94

Table 5: Release Kinetics of Salmeterol Ethosomes of all Formulations F1 to F5

Model	F1		F2		F3		F4		F5	
	r^2	m	r^2	m	r^2	m	r^2	m	r^2	m
Zero-order	0.744	58.3	0.894	2232	0.008	15.87	0.341	72.77	0.832	1313
First order	0.383	0.072	0.630	0.076	0.146	0.042	0.241	0.033	0.451	0.054
Higuchi's Matrix	0.423	5482	0.878	8769	0.034	321.0	0.192	515.4	0.783	8742
Korsmeyer-Peppar	0.724	2.261	0.775	2.467	0.468	1.680	0.556	1.782	0.921	2.632

Table 6: Release Kinetics of Salmeterol Ethosomes of Formulation F6 - F8

Model	Equation	F6		F7		F8	
		r^2	m	r^2	m	r^2	m
Zero order	Mo-Mt=kt	0.891	15.62	0.878	154.3	0.846	2134
First order	InM=InMo	0.481	0.052	0.465	0.051	0.399	0.061
Higuchi's Matrix	$M_0 - M_t$ = kt1/2	0.798	1057	0.848	1067	0.899	11409
Korsmeyer-Peppar	log (M_0-M_t)= log k + n logt	0.782	2.041	0.761	2.044	0.654	2.432

greater (P G .01) than liposomal equation 5. This might imply that ethanol improves opioid permeation throughout the layers of the skin [Table 4 & Figure 3].

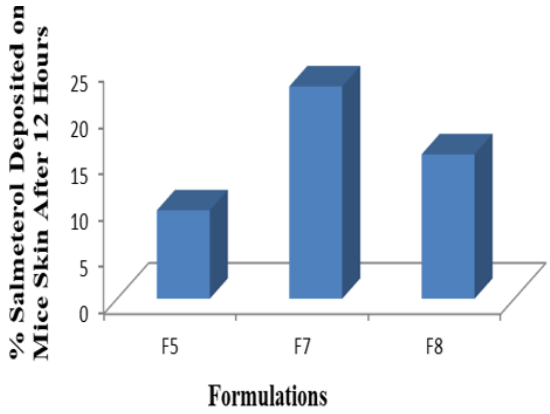

Figure 3: Percentage of SS Deposited on Mice Skin *In Vitro* after 12 Hours of Extracting Different Control, Liposomal, and Ethosomal Formulas with 50% Hydroalcoholic Solution at 37ºC ± 0.5ºC

Statistical analysis of previous findings (i.e., the proportion like Stratum corneum penetrated via rodents epidermis now since 24 hrs. Such study results could explain the phenomenon of that in vitro epidermis accumulation through distinct equations. The proportion like salmeterol transferred through epidermis through the liposomal and even from ethosomal transfer of such opioid through liposomes but rather ethosomes through into stratum corneum bypasses the most barrier of about permeation of drugs, that either significantly enhances skin delivering. Drug entrapment could greatly enhance epidermis accumulation. However, several factors may influence a portion where this position enhances transdermal flux, such as the release of drugs from vesicles within the stratum corneum. The speed but also quantity of set to release opioids is indeed a balancing act among two factors: Opioid affinity of about vesicles, as well as solubility of the drug through fatty acid of a stratum corneum.

Release Order Kinetics

A method like the secretion kinetic model has been analyzed to fit permeability statistics towards the zero-order, first-order, and Higuchi diffusion designs [Table 5 & Table 6].

The whole permeability profile pages accommodate a Higuchi diffusion model, or a linear relationship has been found here between the amount of the drug set to release and the square root of time. It can be indicated that such vacuole did act just like reservoir system design, such as the continuous deployment of an encapsulated drug.

CONCLUSION

The presence of glycerol within the water-soluble storage area of an ethosomal vacuole favors an encapsulation like salmeterol but also improves its permeability through the epidermis like newborn baby rodents because of synergic activity like ethanol, vacuole, as well as epidermis fatty acid. Ethosomal system designs have provided higher quantities like salmeterol at controlled drug release percentages through rodents' epidermis, just as iconic liposomes are. Opioid flux virtues like ethosomal have been substantially higher (P G .01) than those of liposomal formulation 5. They might imply certain ethyl improves opioid permeation from across layers of skin. Of fully ready ethosomal preparations, the very best opioid flux (22.83 ± 0.56 $\mu g/cm^2/h$) has been achieved with 22.83 ± 0.56. The release kinetics mechanism has been evaluated by fitting the permeation data to the zero-order, first-order, and Higuchi dispersion designs. The whole permeability profile pages provide a higuchi dispersion concept, or a linear relationship has been found here between the amount of the drug set to release and the square root of time.

ACKNOWLEDGEMENT

We would like to thank our Principal, sir Dr.K.Srinivas & Dr. M. Pradeep Kumar (HOD & Department of Pharmaceutics) Vasavi institute of pharmaceutical sciences, Vasavi Nagar, Peddapalli (Village), Sidhout (Mandal), YSR Kadapa for supporting and guiding us for writing this research article.

Funding Support

The authors declare that they have no funding support for this study.

Conflict of Interest

The authors declare no conflict of interest in this study.

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Cite this article: Sravani M, Pradeep Kumar M, Satrasala Neelima. **Formulation and Evaluation of Transdermal Delivery of Salmeterol Via Ethosomes**. Int. J.Exp. Biomed. Res. 2022; 1(3): 127-135.

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