Journal of Cardiovascular Disease Research

ISSN: 0975-3583, 0976-2833 **VOL14, ISSUE 08, 2023**

Preparation, Optimization, Compatibility Study, and Evaluation of *In-Vitro and In-Vivo* Release Study of Aripiprazole Pronisome.

Prashant S. Misal[1a*], Sampat D. Nawale[2], Manoj Shirbhate[3],

1a. Associate Professor, Shri Ganpati Institute of Pharmaceutical Sciences and Research, Tembhurni 413211 Research Scholar, Sunrise University, Alwar, Rajasthan 301028

2. Principal, Delight Institute of Pharmacy, Pune 412216

3. Principal, Amrutvahini Institute of Pharmacy, Sangamner 422608

Abstract:

Coagulation fractionation techniques have also been developed for transdermal proniosome arrays using various nonionic surfactants. Span-60 proniosome has lower HLB value, longer alkyl chain and higher phase transition temperature, resulting in higher resistance (94.13 ± 4.76). The addition of LDL cholesterol and lecithin also increases the strength of the bilayer.With the Twain method, the vesicle size decreases and increases with delay and recall. Low polydispersity index and high zeta potential were found in the Pronisome preparation. TEM studies confirmed perfectly round vesicles. IR studies have confirmed that there are no drug interactions in the body and that no drug is blocked. The release kinetics of Pronisome was confirmed to be slower than control. Aripiprazole in 30% PEG. Additionally, Span's emission rate is lower than Tween's, which may be due to the lipophilicity of Span and aripiprazole. Release data favor the Higuchi version, which shows that drug release is controlled by diffusion. The transdermal flow of aripiprazole is highest as it passes through the pores and skin of closed excised rats with the Span 60 system.

Introduction

Pronisome are dry formulations of water-soluble carrier particles coated with surfactants. They rehydrate within a few minutes and are then agitated in a hydrothermal environment to form a liposomal dispersion. The main purpose of developing emission control and target emission dosing profiles is to improve the therapeutic effect of the drug, increase the plasma concentration of the drug, increase the potency and reduce the side effects to ensure the safety of the drug. The main purpose of the new drug vesicle product is to ensure that the drug concentration meets the body's needs throughout the treatment period and to create a controlled and focused online exercise. The drug is encapsulated in vesicles.

This will ensure that the effects of the drug continue. In 1965, Bingham reported for the first time that there is organic matter in the cysts in our body. Targeted drug delivery is a

ISSN: 0975-3583, 0976-2833 VOL14, ISSUE 08, 2023

type of delivery of therapeutic drugs to tissues. The medicine contained in the capsule enters the recipient's organs or other parts of his body. Various delivery systems have been used to deliver drugs to various parts of the body, including tissues and organs, including niosomes, proniosomes, liposomes, microspheres, electrosomes, and phytosomes.This vesicular drug delivery involves delivering the drug to the target. Vesicular drug delivery includes B. Colloidal particles form concentric bilayers in which amphiphilic molecules are trapped in aqueous compartments. Amphiphilic molecules such as surfactants (non-ionic), phenols and phosphatidylcholines (phosphatidylserine, etc.) are given together with cholesterol or one at a time.Proniosomes prevent problems associated with niosomes such as chemical fusion, aggregation, physical stability, precipitation, and aggregate leakage..

Experimental

Preparation of niosomes

Liposomes are arranged by phase separation. First, heat all additives using a small amount of alcohol (without ethanol) at 65 ± 3°C to make a sol, micelles are not needed. After the addition of the aqueous portion, the left portion of the W/O microemulsion is formed, which binds the water droplets together, using an interfacial film of surfactant dispersed in the continuous solid phase. As the proniosome gel cools, the solubility (limited weight) of surfactant and gelling agent in the solvent decreases, forming a layered micelle shape. The cross-sectional transfer temperature plays an important role in proniosome gelation.Span20 and Span 80 have a minimum transition temperature of 16°C and -12°C respectively, so they are liquid at room temperature and cannot produce low cholesterol or cholesterol. In general, 20-30 mole percent of cholesterol is required. Span 40 (42°C) and Span 60 (53°C) have high transition temperatures and therefore form gels with or without LDL cholesterol. They are solid at room temperature and can act as gelling agents themselves. These gels are heat reversible in nature.Gel formation of nonionic surfactants depends on many factors such as their structure, critical packing parameter (CPP), hydrophilic-lipophilic stability (HLB), and presence of LDL cholesterol [30]. CPP (v/lca0) depends on the ratio of the level of hydrophobic tissue (v) to the length of the hydrophobic tissue (lc) and the proximity of the hydrophilic tissue (a0). CPP values between 0.5 and 1 are chosen for vesicle formation, values below 0.5 indicate formation of round micelles and higher values (>1) indicate formation of reverse micelles.Statistical analysis is demonstrated by Dunnet with multiple comparisons.

ISSN: 0975-3583, 0976-2833 VOL14, ISSUE 08, 2023

ANOVA ($p<0.05$) was used to analyze bile and non-bilious blebs and transdermal blebs with aripiprazole tablets and business models. t-test was also used to compare AUC values between preparations.

Table 1: Proniosome formulations with their compositions (mg)

Formulation Code	Type of surfactant	Surfactan (mg)	Soya Lecithin (mg)	Cholesterol (mg)	Aripiprazole (mg)
PS- 20	Span20	1800	1800	200	50
PS- 40	Span40	1800	1800	200	50
PS- 60	Span60	1800	1800	200	50
PS- 80	Span80	1800	1800	200	50
PT- 20	Tween20	1800	1800	200	50
PT- 60	Tween60	1800	1800	200	50
PT- 80	Tween80	1800	1800	200	50
PS- L	Span60	900	1800	200	50
PS- H	Span60	2700	1800	200	50
PL- L	Span60	1800	900	200	50
PL- H	Span60	1800	2700	200	50
PC- L	Span60	1800	1800	100	50
PC- H	Span60	1800	1800	300	50

RESULT AND DISCUSSIONS

Aripiprazole liposomes are also being developed, optimized and evaluated for their transdermal delivery potential to overcome the problems associated with oral administration. Proniosome gels are prepared from alkyl esters (such as spin and Tween), LDL cholesterol and soy lecithin using a variety of nonionic surfactants. All of these ingredients are listed in the FDA and GRAS Inactive Ingredient Database. Span and Tween are non-toxic, biocompatible non-ionic surfactants..

Optimization of niosomes

The formulation was optimized by comparing the following parameters: small vesicle

ISSN: 0975-3583, 0976-2833 VOL14, ISSUE 08, 2023

size, high encapsulation efficiency and transdermal flow. Vesicle sizes, polydispersity indices, zeta potential and encapsulation efficiency for various vesicle formulations are shown in Table 2.

Table 2: Different proniosome formulations and their encapsulation efficiency, vesicle size, polydispersity index, and zeta potential

Formulation code	Encapsulation efficiency (%)	Mean Vesicle size ± SD (nm)*	PDI	Zeta potential (mV)
PS- 20	85.23 ± 3.45	486.40 ± 3.84	0.246	-56.2 ± 7.67
PS- 40	92.43 ± 2.76	941.40 ± 3.23	0.297	-52.7 ± 7.91
PS- 60	94.13 ± 4.76	858.30 ± 2.42	0.310	-47.3 ± 7.63
PS- 80	89.17 ± 3.46	716.80 ± 4.37	0.209	-48.5 ± 5.60
PT- 20	52.45 ± 7.89	338.80 ± 6.43	0.281	-41.3 ± 6.37
PT- 60	58.13 ± 4.34	342.90 ± 5.35	0.293	-40.9 ± 5.44
PT- 80	62.43 ± 5.67	284.00 ± 5.43	0.284	-37.4 ± 7.68
PS- L	90.23 ± 7.99	821.85 ± 7.89	0.134	-45.6 ± 3.42
PS- H	94.78 ± 3.76	899.74 ± 6.84	0.243	-47.8 ± 4.16
PL- 1:2	89.45 ± 4.87	999.00 ± 6.34	0.231	-49.9 ± 7.62
PL- 1:3	96.13 ± 9.45	1084.00 ± 9.45	0.245	-51.4 ± 11.9
PC- L	82.45 ± 3.45	842.20 ± 2.67	0.048	-55.1 ± 9.73
PC- H	88.43 ± 1.54	1289.00 ± 4.30	1.000	-52.3 ± 7.71

*Mean± SD, n=3

Niosomes Evaluation

a. Efficiency of inclusion:-Percent entrapment efficiency was found to depend on the type of surfactant used, its alkyl chain length, HLB values, and phase transition temperature (Table 2).

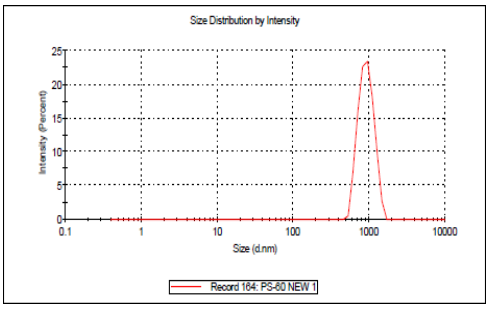


Fig 1: Vesicle size of hydrated PS-60 Pronisome formulation

ISSN: 0975-3583, 0976-2833 VOL14, ISSUE 08, 2023

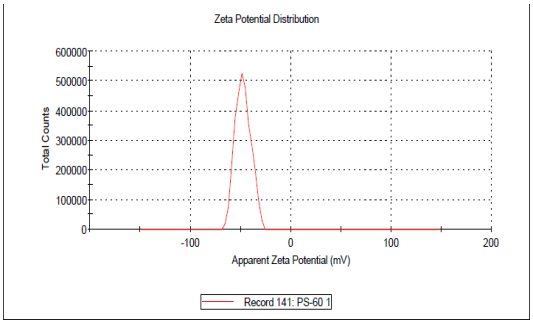


Fig 2: Zeta potential of hydrated PS-60 Pronisome formulation

a. *In-vitro* release study

In vitro, drug release studies from proniosome formulations were performed in locally prepared Franz diffusion cells using egg membranes.

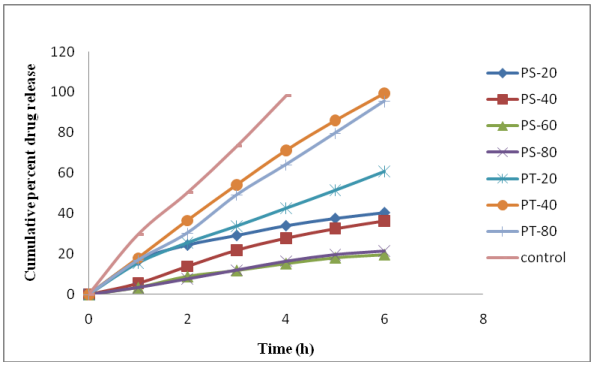


Fig 3: *In-vitro* release of Aripiprazole from niosomes through the egg membrane

Figure 3 shows that complete drug release (100%) from the control (30% aripiprazole in PEG) occurred within 4 hours compared to aripiprazole-niosome, demonstrating the activity of the niosome. acting acting This is because aripiprazole is lipophilic enough to promote lipophilic cleavage, which slows the release of aripiprazole from vesicles. When Tween and Span formulations were analyzed, aripiprazole was found to be released more slowly than Span because Tween released both hydrophilic and lipophilic aripiprazole faster.In most formulations, the initial phase is dependent on desorption of aripiprazole from the vesicle surface, while the late phase is controlled by diffusion from swelling of the nasal bilayer. This may be particularly relevant if the initial saturation of the dermis is achieved by faster drug delivery through blood vessels to maintain the high concentration gradients required for effective drug transport into the blood. After the initial analysis of the ps-60 formulation, it was decided to conduct morphology, excipient compatibility studies, drug emission kinetics, irritation studies, occlusive studies, ex vivo permeation studies and in vivo studies.BC

ISSN: 0975-3583, 0976-2833 VOL14, ISSUE 08, 2023

Morphology The morphology of the examined hydrated proniosome (PS-60) was analyzed by light microscopy (parent 4) and transmission electron microscopy (TEM).A photomicrograph of the proniosome preparation (PS-60) is shown in Figure 2. True TEM results showing correct formation are defined as spherical muscles with sharp edges. The spherical structure is unique due to the amphiphilic nature of surfactants.

Fig 4: Optical photo micrograph of PS-60 niosomes after hydration (40X)

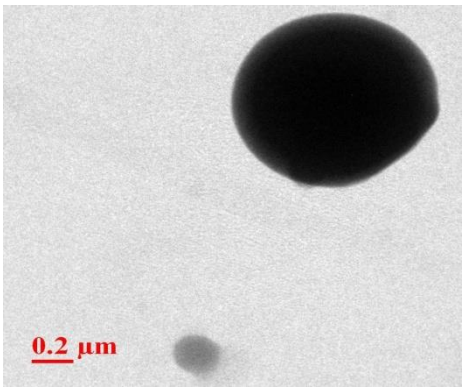
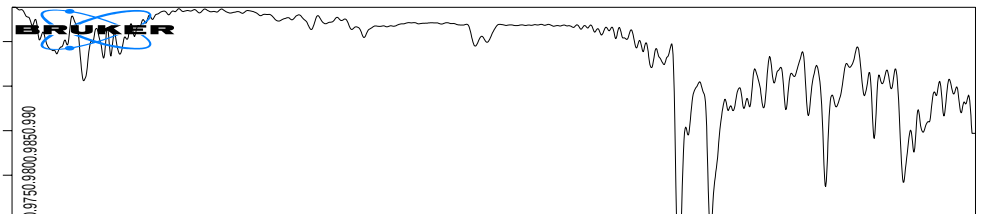


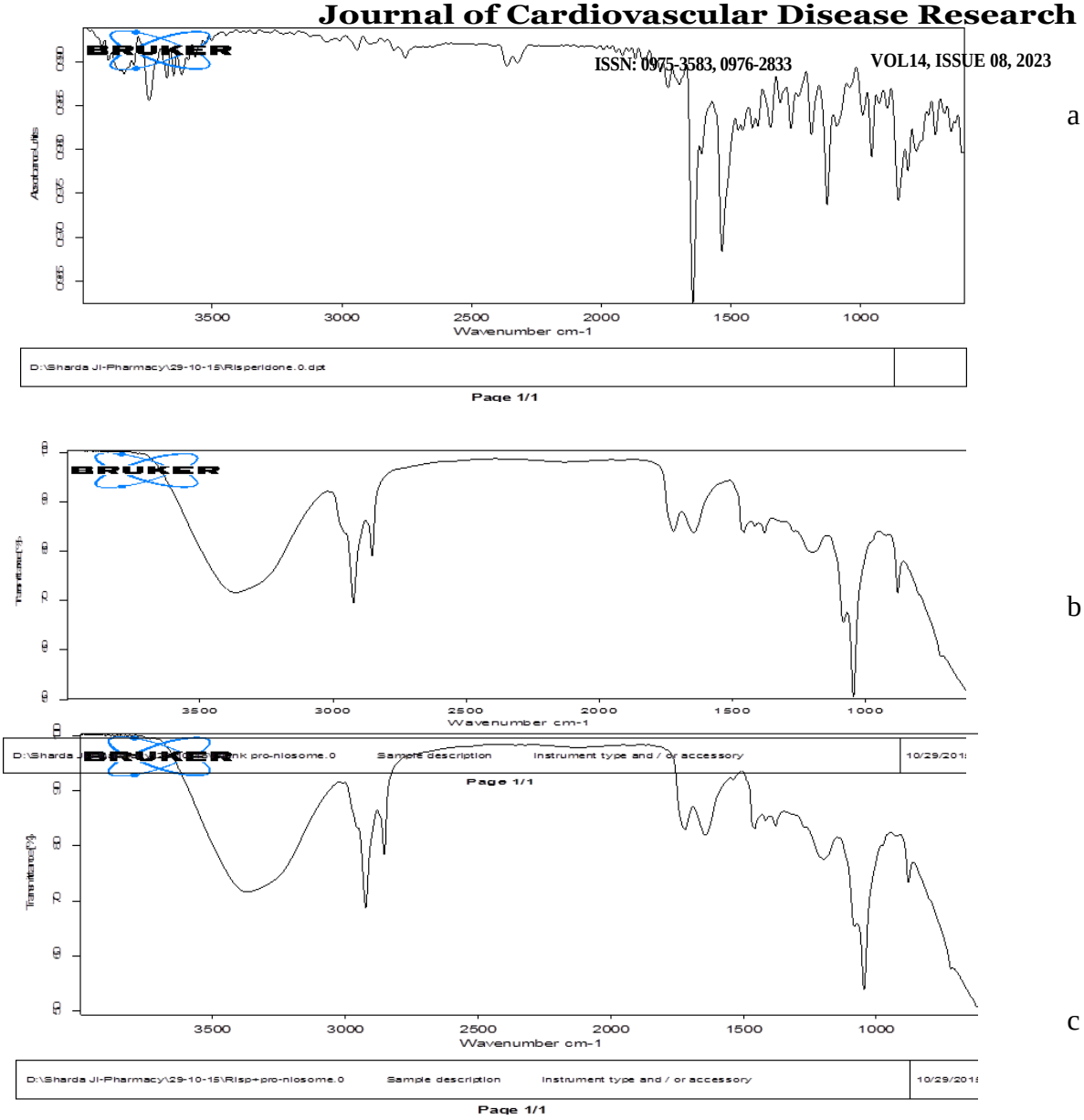
Fig 5: Transmission electron micrograph ofPS-60 proniosome

b. Drug excipient compatibility study and infra-red Spectroscopy

Figure 5 shows the FTIR spectra of aripiprazole, Span 60, soy lecithin and compound body. The FTIR spectrum of aripiprazole shows 1646 cm-1 (C=O stretch), 1534 cm-1 (N-H stretch), 1128 cm-1 (C-H stretch), 853 cm-1 (C-H stretch, aromatic family) and 3744 cm-1. 1. Determine the height. cm-1 (K-H pressure).Span 60, 1200 cm-1 (aliphatic), 1734 cm-1 (cyclic five-membered ring), 1400 cm-1 (-CH3), 2928 cm-1 (aliphatic C-H tense, asymmetrical), 2800 cm Height specifications - 1 (aliphatic C-H stretch, symmetrical) and 3400 cm-1 (O-H stretch). Analysis of body accumulation of aripiprazole, Span 6.0 and soybean lecithin showed that the characteristics of the aripiprazole peak in body accumulation were similar to those seen in the male or female aripiprazole spectra, but no change in the FTIR spectra. No change was observed in FTIR. spectrum.Chemically indirect interactions between them have been observed. FTIR spectra of empty vesicles and aripiprazole-loaded vesicles are shown in Figure 6. FTIR spectra of empty vesicles and aripiprazole-loaded vesicles are blank.



ISSN: 0975-3583, 0976-2833 VOL14, ISSUE 08, 2023



a

b

c

Fig 7: IR spectra (a) Aripiprazole (b) blankniosomes (c) niosomes containing Aripiprazole

c. Drug release kinetics

Release data from the ps-60 formulation is used for a specific kinetic equation to determine the sequence and mechanism of drug release. The correlation coefficients show that the oscillation curve fits the Higuchi model (R2 = 0.9957). The emission index n for the Korsmeyer-Peppas model is 0.7751 (0.7751.43). This is the abnormal release behavior shown in Table III and also indicates that the release process is diffusion controlled.

Table 3: Correlation coefficient for Aripiprazole release through different kinetic models

ISSN: 0975-3583, 0976-2833 VOL14, ISSUE 08, 2023

Release Kinetics	Zero-order		First-order		Higuchi model		Korsemeyer Peppas model	
	K	R^2	K	R^2	K	R^2	N	R^2
	3.185	0.971	0.137	0.8424	11.223	**0.9957**	0.7751	0.9738

d. Stability studies

It can determine the effect of various environmental factors such as temperature, humidity and light on chemical stability. Table IV shows that the encapsulation efficiency and vesicle level of the PS 60 formulations stored in the refrigerator and at room temperature were not significantly different ($p < 0.05$).

Table 4: Vesicle size and entrapment efficiency of niosomes (PS-60) after 90 days of storage

Temperature (°C)	Particle size (nm)		Entrapment efficiency (%)	
	0months	**3months**	**0months**	**3months**
4 ± 1 °C	858.30 ± 2.42	860.30 ± 3.23	94.13 ± 4.76	93.78 ± 4.53
25 ± 2 °C	858.30 ± 2.42	863.93 ± 3.86	94.13 ± 4.76	92.57 ± 6.74

n=3($p<0.05$)

e. Irritation/sensitivity studies

Supplementary studies were performed in male Wistar rats (n = 3; body weight 200-250 g). Formalin has become a common chemical. Mice were scored for erythema and edema [57,135]. Table 5 shows that the frequency of erythema and edema was reduced in mice treated with Proniosome compared to mice treated with the standard stimulant formalin (0.33 ± 0.471; $p<0.05$). We can complete tasks such as: Training is user-friendly and secure.

Table 5: Average response of skin irritation scores following application of niosomes formulations (PS-60)

Average response (Mean score)	Formalin treated (standard irritant)	Formulation treated

ISSN: 0975-3583, 0976-2833 VOL 14, ISSUE 08, 2023

Erythema	2.33 ± 0.471	0.33 ± 0.471
Edema	2.66 ± 0.471	0.33 ± 0.471

Rats,n=3/group

f. *Ex-vivo* permeation studies

Nanobodies can be hydrated with moisture in the skin to shape the nanobody, thereby altering the transport of drugs through the skin. Adsorption and fusion of vesicles on the skin increase drug penetration and modify the stratum corneum barrier, allowing nonionic surfactants to act as penetration agents. In particular, it affects the density of lipids in the extracellular region of the stratum corneum. In addition, the lipid bilayer acts as a rate-limiting factor for the penetration of drugs. The threshold (flux) value of aripiprazole became very specific across the egg membrane and in the skin (Figure 1).

8), displaying time in a wall-mounted life. The bonding and fusion of the vesicles with the pores and skin surface leads to a better effect due to direct drug transport by the vesicles. From Table 5.6, 60 formulations were found to have the best flow (169,851 ± 8. 53 µg/cm2/h) from mouse skin. Liposomes containing tween showed lower flux than length. This may be because it reduces lipophilicity, reduces fusion with the skin, and reduces permeability.

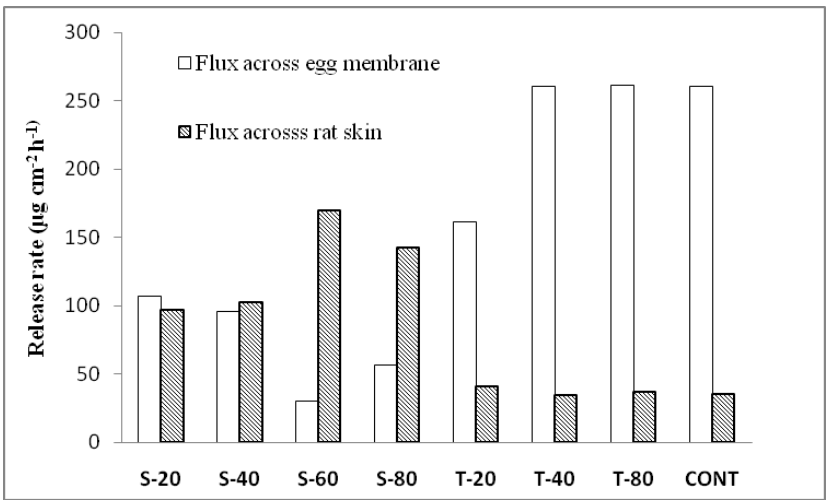


Fig 8: Comparative evaluation of flux of Aripiprazole from niosomes across egg membrane and excisedrat skin

Table 6: Flux of Aripiprazole from different niosomes

ISSN: 0975-3583, 0976-2833 VOL14, ISSUE 08, 2023

Formulation Code	Flux(μgcm^{-2}h^{-1})	
	Egg membrane	**Rat skin**
PS20	106.950 ± 2.31	97.132 ± 3.42
PS40	96.115 ± 6.43	102.472 ± 5.34
PS60	30.706 ± 3.14	169.851 ± 2.136
PS80	56.780 ± 4.52	142.783 ± 3.24
PT20	161.638 ± 3.54	40.830 ± 5.87
PT60	260.625 ± 2.38	34.871 ± 3.44
PT80	261.539 ± 5.44	36.718 ± 3.57
Control	261.015 ± 4.57	35.120 ± 4.83

g. Occlusion studies

Table 7 shows the permeability coefficients of aripiprazole liposomes from excised mouse vaporized skin under occlusive and non-occlusive conditions. Hydrophilic and lipophilic drugs often exhibit transdermal absorption under occlusive conditions. Therefore, nanocores made under closed conditions have good flux values (169.85 ± 8.7 μg cm-2h-1), permeability coefficients (33.85 ± 8.7 μg cm-2h-1).97 × 10-3 cmh-1) tab enlargement factor (4,836).

Table 7: Permeability study of optimized formulation of Aripiprazole

Formulation	Flux (μgcm^{-2}h^{-1})	Permeability Coefficient (cmh^{-1})	ER
Control	35.12 ± 5.80	7.024×10^{-3}	1
PS-60(non occlusive)	129.28 ± 6.5	25.85×10^{-3}	3.681
PS-60(occlusive)	169.85 ± 8.7	33.97×10^{-3}	4.836

ER=enhancement ratio, (n=3)

h. *In-vivo* and HPLC studies

In vivo analysis was performed in rabbits and plasma samples were analyzed by high performance liquid chromatography. Chromatogram length for the reaction of aripiprazole

ISSN: 0975-3583, 0976-2833 VOL14, ISSUE 08, 2023

API, biliary liposomes, biliary liposomes, transdermal liposomes, and oral aripiprazole is 10. Aripiprazole and diltiazem (internal form) have a retention time of 4 and 6 minutes, respectively.

Fig 9: *In-vivo* study in rabbit

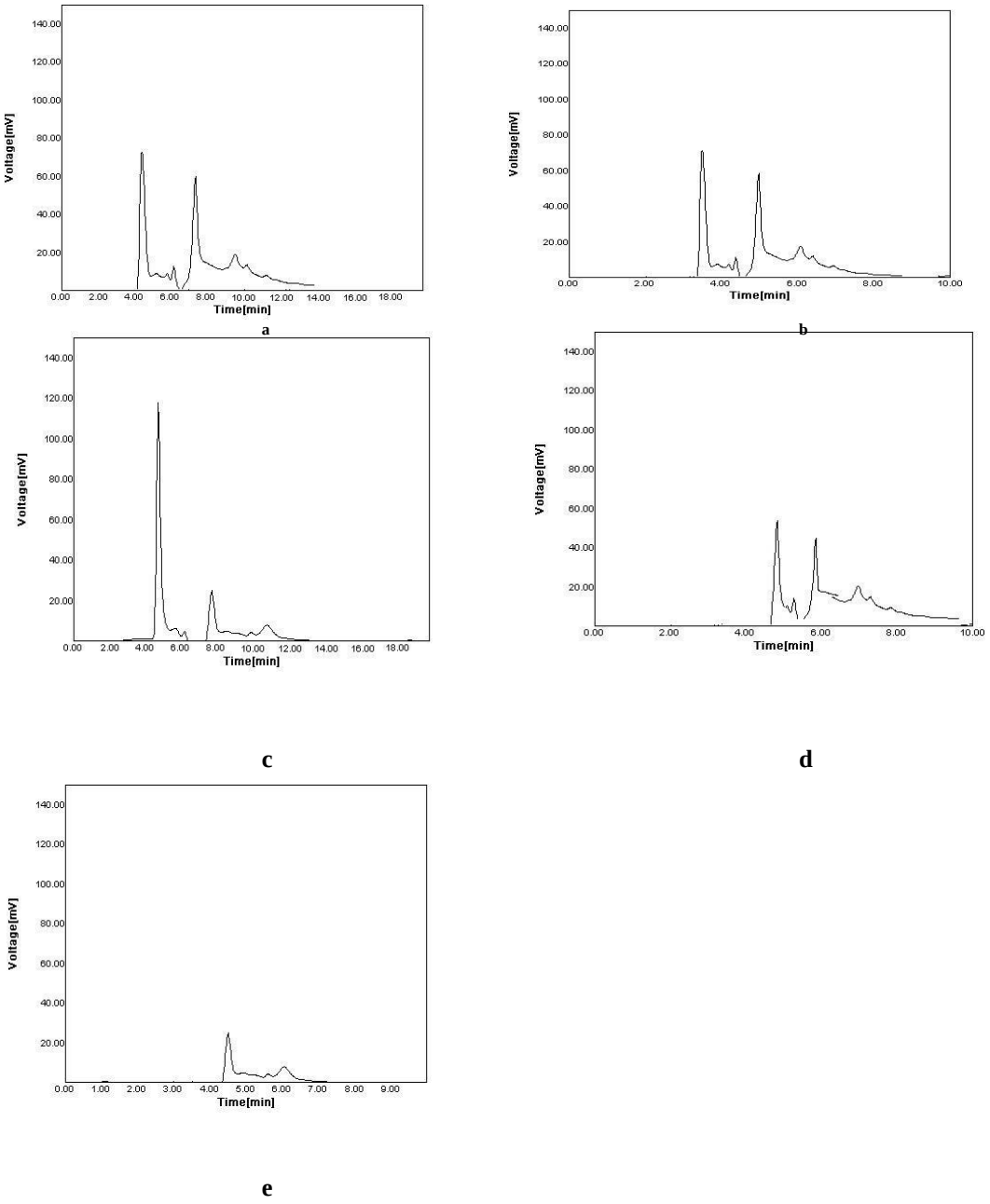


Fig 10: Chromatograms for (a) Aripiprazole, API (b) niosomes (c) niosomes containing bile salt (d) marketed Aripiprazole oralsolution (e) transdermal niosomes

ISSN: 0975-3583, 0976-2833 VOL14, ISSUE 08, 2023

The plasma drug focus profiles of various formulations are provided in desks 8 and Fig 11. The pharmacokinetic parameters for Aripiprazole API marketed machine, niosome with and without bile salts, and proniosome gels are validated in desk 8.

Table 8: Plasma drug concentrations of different formulations

Time (hr)	API	Marketed Aripiprazole oral solution	Niosomes with bile salt	Niosomes without bile salt	Transdermal niosomes
1	125.53 ± 7.6	88.12 ± 9.5	137.18 ± 11.8	95.34 ± 10.2	86.47 ± 8.7
4	238.14 ± 9.1	214.51 ± 10.2	296.42 ± 8.4	191.72 ± 9.6	149.58 ± 10.8
8	156.86 ± 5.4	165.34 ± 12.7	187.76 ± 9.2	232.64 ± 13.5	198.65 ± 13.2
16	75.47 ± 9.3	145.62 ± 9.1	102.24 ± 7.1	167.52 ± 10.3	122.43 ± 11.3
24	23.92 ± 10.8	87.35 ± 11.4	65.15 ± 9.7	101.46 ± 12.6	68.28 ± 10.1

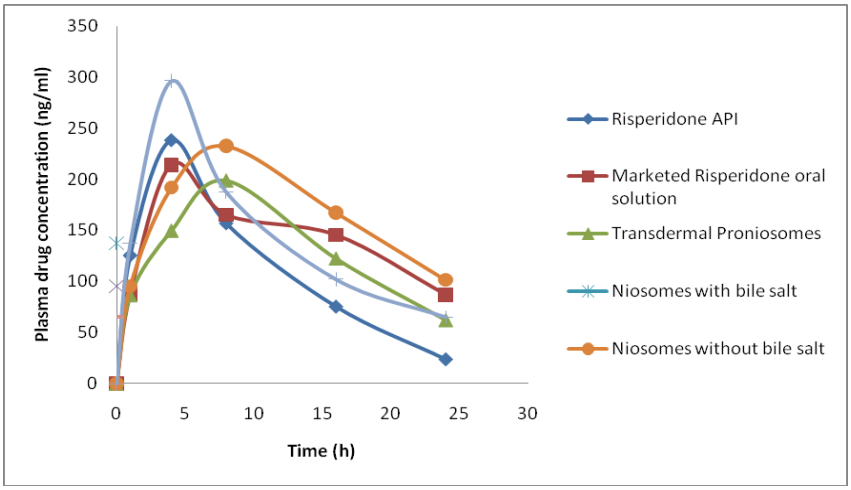


Fig 11: *In-vivo* studies of niosomes

ISSN: 0975-3583, 0976-2833 VOL14, ISSUE 08, 2023

Table 9: Summary of mean pharmacokinetic parameters after oral administration of Aripiprazole API, marketed oral solution, niosomes with and without bile salts, and niosomes patch (PS-60)

Pharmacokinetic parameters	Aripiprazole API	Marketed Aripiprazole oral solution	Niosomes with bile salt	Niosomes without bile salt	Transdermal proniosome
C_{max}[a](ng/mL)	238.14 ± 9.1	214.51 ± 10.2	296.42 ± 8.4	232.64 ± 13.5	198.65 ± 13.2
T_{max}[b](h)	4	4	4	8	8
$AUC_{(0\text{-}24h)}$[c] (ng.h/mL)	2608.08 ± 3.5	2464.09 ± 6.2*	2666.52 ± 5.8*	2738.35 ± 6.5*	2278.33 ± 4.1*
$AUC_{(0\text{-}\infty h)}$[d] (ng.h/mL)	2836.25 ± 5.1	2836.16 ± 4.9	3265.47 ± 5.2*	3887.21 ± 7.5*	2568.96 ± 4.7*
$t_{1/2}$[e](h)	0.658	0.563	0.532	0.759	0.589
V_d[f]	9.92	10.75	10.66	10.97	10.49
F%[g]	105	100	108	111	92
MRT last (h)[h]	9.45 ± 0.38	9.88 ± 0.51	12.79 ± 0.11	23.46 ± 0.39	41.63 ± 0.57
MRT∞ (h)	12.36	38.17	17.59	26.89	47.44

[a]Peak plasma concentration, [time] of maximum plasma concentration, the [area] under the curve for time 0 to24h, [area] under the curve for time 0 to infinity, [elimination] half-life, [volume] of distribution, [relative]bioavailability, [mean] residence time,*p<0.05, ANOVA followed by Dunned multiple comparison testswasapplied tocompare theformulations with API and marketedformulation

Blisters containing bile salts showed faster absorption, reaching a maximum plasma concentration (Cmax) of 296.42 ng/ml after 4 hours, and blebs containing bile salts also showed a very good Cmax of 232.64 ng/ml. he taught. The Cmax of both biliary and non-biliary vesicle preparations reached the level of commercial preparations (Section 214).

5 ng/ml). The most alarming level of the drug in plasma was 198.65 ± 3.2 ng/ml after liposome transdermal administration. Cmax is determined by the dose, rate of absorption and excretion and is generally related to the depth of the pharmacological response.

Doses were similar for all 5 compounds, suggesting that better Cmax values are associated with greater drug absorption. Bile uptake into vesicles of M cells in Peyer's patches in intestinal lymphoid tissue is said to increase biofilm permeability through

ISSN: 0975-3583, 0976-2833 VOL14, ISSUE 08, 2023

transcytosis, thereby promoting bile resorption and causing Cmax to be too high. To do. This shows that you accept it. The area under the curve (AUC) represents the amount of drug absorbed (bioavailability) of the dosage form.

Summary and Conclusion

In vivo studies in rabbits have shown that Cmax is higher for liposomes containing bile salts (296.42 ng/ml) and liposomes without bile salts (232.64 ng/ml) compared to the commercial preparation. He was killed.

Proniosomes confirmed Cmax of 198.65 ± 13. In the absence of bile salts and proniosome gel, T increased from 4 hours to 8 hours with niosome and niosome mean doubling time (MRI) compared to aripiprazole API. The area under the curve (AUC) was adjusted to improve vesicle assembly in the presence and absence of bile salts. Thus, it is clear that engineered aripiprazole liposomes show long-term relative bioavailability and excellent plasma drug concentrations (Cmax).

The presence of bile salts in the vesicles easily enters the vesicles quickly into the biomembranes. However, in the absence of bile, niosomes and proniosomes remain in the body for a long time. All of the above studies showed that the nonionic surfactant reduced the initial concentration of the drug and the bioavailability was reasonable, the relative bioavailability of non-biliary cysts increased by 111% and the relative bioavailability of nodular vesicles increased by 108%. . is based on this concept only. The transdermal system also exhibits a relative bioavailability of 92%.

It can also be used as an alternative to oral administration.

References

1. Arzani G, Haeri A, Daeihamed M, Kaboutaraki HB, Dadashzadeh S. Niosomal carriers enhance oral bioavailability of carvedilol: effects of bile salt-enriched vesicles and carrier surface charge. Int J Nano medicine 2015; 10:4797-813.
2. Khan MI, Madni A, Ahmad S, Khan A, Rehman and M, Mahmood MA. ATR-FTIR based pre and post-formulation compatibility studies for the design of niosomal drug delivery system containing non-ionic Amphiphiles and chondro protective drugs. J Chem Soc Pakistan 2015;37(3):527-34.
3. Shaker DS, Shaker MA, Hanafy MS. Cellular uptake, cytotoxicity and in-vivo evaluation of tamoxifen citrate loaded niosomes. Int J Pharm 2015; 493:285-94.
4. Mokale VJ, Patil HI, Patil AP, Shirude PR, Naik JB. Formulation and optimization of famotidine proniosomes: an *in-vitro* and *ex-vivo* study. J Exp Nano sci 2016;11(2):97-110.

ISSN: 0975-3583, 0976-2833 VOL14, ISSUE 08, 2023

5. Fang JY, YuS Y, Wu PC. *In vitro* permeation of estradiol from various proniosomes formulations. IntJ Pharm2001; 215:91-9.
6. Kumhar SK, JainSK, Pancholi SS, Agrawal S, Saraf DK, Agrawal GP. Provesicular transdermal drug delivery system of Ethinyl estradiol and levonorgestrel for contraception and hormone replacement therapy. Indian J Pharm Sci 2003;65(6):620-7.
7. Alsarra IA, Bosela AA, Ahmed SM, Mahrous GM. Proniosomes as a drug carrier for transdermal delivery of ketorolac. Eur J Pharm Biopharm 2005; 59:485-90.
8. Alsarra IA. Evaluation of proniosomes as an alternative strategy to optimize piroxicam transdermal delivery. J Microencapsul 2009;26(3):272-8.
9. Thakur R, Anwer MK, Shams MS, AliA, Khar RK, Shakeel F,etal. Proniosomal transdermal therapeutic system of losartan potassium: development and pharmacokinetic evaluation. JDrug Target 2009;17(16):442-9.
10. Aboelwafa AA, El-Setouhy DA, Elmeshad AN. Comparative study on the effects of some polyoxyethylene alkyl ether and sorbitan fatty acid ester surfactants on the performance of transdermal carvedilol proniosomal gel using experiment tal design, AAPS Pharm Sci Tech 2010;11(4):1591-602.
11. El-Laithy HM, Shoukry O, Mahran LG. Novel sugar esters proniosomes for transdermal delivery of vinpocetine: Preclinical and clinical studies, Eur J Pharm Biopharm 2011; 77:43-5.
12. Abbas HK, Ienas F, Hussein AH, Al-Yousuf MD, Shaheed DQ. Preparation and *in-vitro* evaluation of metoprolol tartrate proniosomal gel. Kerbala J Pharm Sci 2013; 6:153-63.
13. Rahman SA, Abdelmalak NS, Badawi A, Elbayoumy T, Sabry N, El Ramly A.Formulation of tretinoin-loaded topical proniosomes for treatment of acne: *in-vitro* characterization, skin irritation test, and comparative clinical study. Drug Deliv 2015; 22(6):731-9.
14. Wen MM, Farid RM, Kaseem AA. Nano-proniosomes enhance thetransdermal delivery of mefenamic acid. J Liposome Res 2014;24(4):280-9.
15. Yongtai Z, Kai Z, Zhonghua W, Teng G, Beini Y, Mingyun L, et al. Evaluation of transdermal salidroside delivery using niosomes via *in-vitro* cellular uptake. Int J Pharm 2015;478(1):138-46.
16. El-Maghraby GM, Ahmed AA, Osman MA. Penetration enhancers in proniosomes as a new strategy for enhanced transdermal drug delivery. Saudi Pharm J 2015; 23:67-74.

ISSN: 0975-3583, 0976-2833 VOL14, ISSUE 08, 2023
17. Xiuhua R, Xinliang M, Lei C,etal. Non-ionic surfactants are strong inhibitors of Cytochrome P450 3A biotransformation activity *in-vitro* and *in-vivo.* Eur J Pharm Sci 2009; 36:401-11.
18. Gianasi E,Cociancich F,Uchegbu IF,etal. Pharmaceutical and biological characterization of a doxorubicin-polymer conjugate (PK1) entrapped in sorbitan monostearate span 60 niosomes. Int J Pharm 1997; 148:139-48.
19. Kumar MS, Smith AA, Vasagam GA. Development of analytical methods for risperidone by UV spectrophotometry. Int J Pharm Sci Res 2010; 1:122-6.
20. Manconi M, Valenti D, Sinico C, et al. Niosomes as carriers for tretinoin II. Influence of vesicular incorporation on tretino in photostability.Int J Pharm 2003; 260:261-72.
21. Yasam VR, Jakki SL, Natarajan J, Kuppusamy G. A review on novel vesicular drug delivery: proniosomes. Drug Deliv 2014;21(4):243-9.
22. Vora B, Khopade AJ, Jain NK. Proniosomes-based transdermal delivery of levonorgesteral for effective contraception. J Control Release 1998; 54:49-65.
23. Rahman SA, Abdelmalak NS, Badawi A, Elbayoumy T, Sabry N, El Ramly A, Formulation of tretinoin-loaded topical proniosomes for treatment of acne: *in-vitro* characterization, skin irritation test, and comparative clinical study, Drug Deliv 2015;22(6):731-9.
24. Akhtar M, Imam SS, Ahmad MA, Najmi AK, Mujeeb M, Aqil M. Neuroprotective study of Nigellasativa-loaded oral provesicular lipid formulation:*in-vitro* and *ex-vivo* study. Drug Deliv2014; 21(6):487-94.
25. Draize JH, Woodard G, Calvery HD. Methods for the study of irritation andtoxicity of substances applied topically to the skin and mucous membranes. J Pharmacol ExpTher 1944; 82:377-90.
26. Ibrahim MMA, Sammour OA, Hammad MA, Megrab NA. *In-vitro* evaluation of proniosomes as a drug carrier for flurbiprofen. AAPS Pharm Sci Tech 2008;9(3):782-90.
27. Aravagiri M, Marder SR, Putten TV, et al. Determination of risperidone in plasma by high-performance liquid chromatography with electro chemical detection: application to therapeutic drug monitoring in schizophrenic patients. J Pharm Sci 1993; 82:447-9.
28. Rowe RC, Sheskey PJ, Quinn ME. Handbook of Pharmaceutical Excipients. 6thed. London: Pharmaceutical Press; 2009.
29. ShahR, Eldridge D, Palombo E, Harding I. Optimization and stability assessment

ISSN: 0975-3583, 0976-2833 VOL14, ISSUE 08, 2023
of solid lipid nano particles using particle size and zeta potential. J Phys Sci 2014;25(1):59-75.

30. Yoshioka T, Florence AT. Vesicle (niosome)-in-water-in-oil (v/w/o) emulsions: an*in-vitro* study. Int J Pharm1994;108(2):117-23.
31. Hu C, Rhodes DG. Proniosomes: a novel drug carrier preparation. Int J Pharm1999; 185:23-8.
32. Zidan AS, Mokhtar M. Multivariate optimization of formulation variables influencing flurbiprofen proniosomes characteristics. J Pharm Sci 2011;100 (6):2212-21.
33. Junyaprasert VB, Singhsa P, Suksiriworapong J,etal. Physicochemical properties and skin permeation of span 60/tween 60 niosomes of ellagic acid. Int J Pharm2012; 423:303-11.
34. Balakrishnan P, Shanmugam S, Lee WS, Lee WM, Kim JO, Oh DH, et al. Formulation and *in-vitro* assessment of minoxidil niosomes for enhanced skin delivery. Int J Pharm2009;377(1-2):1-8.
35. Wan LSC, Lee PFS. Studies on the surface film of sorbitan esters at the air/water interface. Can J Pharm1974; 9:82-5.
36. Dash S, Murthy PN, Nath L, et al. Kinetic modeling on drug delivery systems. Acta Pol Pharm2010; 67:217-23.
37. Aungust BJ. Enhancement of Intestinal absorption of Proteins and Peptides. J Control Release 1996; 41:19-31.
38. Schubert R, Jaroni H, Schoelmerich J, et al. Studies on the mechanism of bile salt-induced liposomal membrane damage. Digestion 1983; 28:181-90.
39. Ibrahim MMA, Sammour OA, Hammad MA, Megrab NA. *In-vitro* evaluation of proniosomes as a drug carrier for flurbiprofen, AAPS Pharm Sci Tech 2008;9(3):782-90.
40. Aboelwafa AA, El-Setouhy DA, Elmeshad AN. Comparative study on the effects of some polyoxyethylene alkyl ether and sorbitan fatty acid ester surfactants on the performance of transdermal carvedilol proniosomal gel using experimental design, AAPS Pharm Sci Tech 2010;11(4):1591-1602.
41. Hathout RM, Mansour S, Mortada ND, Guinedi AS. Liposomes as an oculardelivery system for acetazolamide: *in-vitro* and *in-vivo* studies. AAPS Pharm Sci Tech 2007;8(1):1-7.
42. Brittain HG. Profiles of drug substances, excipients, and related methodology.Volume37, Academic Press, Amsterdam; 2012:324-361.

ISSN: 0975-3583, 0976-2833 VOL14, ISSUE 08, 2023

43. Pardakhty J, Varshosaz AR. *In-vitro* study of polyoxyethylene alkyl ether niosomes for delivery of insulin. Int J Pharm 2007; 328:130-41.
44. Csoka G, Marton S, Zelko R, et al. Application of sucrose fatty acid esters intransdermal therapeutic systems. Eur J Pharm Biopharm 2007; 65:233-7.
45. Tiemessen HM, Bodde HE, Mollee H, Junginger HE. Ahuman stratum corneum-silicone membranes and wichto stimulate drug transport under occlusion. Int J Pharm 1989; 53:119-127.
46. Abdelkader H, Alani AW, Alany RG. Recent advances in non-ionic surfactant vesicles (niosomes): self-assembly, fabrication, characterization, drug delivery applications, and limitations. Drug Deliv 2014; 21:87-100.
47. Foroutan SM, Zarghi A, Shafaati A, Khoddam A. Rapid high performance liquid chromatographic determination of risperidone in human plasma. Iran J Pharm Res 2006; 1:37-40.
48. GutierroAI, Franco RG, inventor; Laboratories Farmaceuticos Rovi, SA, Gutierro AI, Franco R G, assignee. Risperidone orpaliperidone implant formulation. Canada Patent CA2874765. 2013 May 31.
49. Badshah A, Subhan F, Rauf K, Bukhari NI, Shah K, Khan S, et al. Development of controlled-release matrix tablet of risperidone: Influence of methocel®-and ethocel®-based novel polymeric blend on *in-vitro* drug release and bioavailability. AAPS Pharm Sci Tech 2011;12:525-33.