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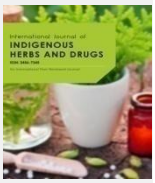

FORMULATION AND EVALUATION OF GANCICLOVIR PROLIPOSOMAL GEL FOR TRANSDERMAL DRUG DELIVERY SYSTEM

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ABSTRACT

Proliposomes are free flowing powder formulations containing water soluble carrier particles coated with phospholipids that immediately form a liposomal dispersion on contact with water in the body. The resulting liposomes may act as a sustained release dosage form of the loaded drugs. Proliposomes are composed of drug, phospholipid and a water soluble porous powder and can be stored sterilized in a dried state. Because of the solid properties, the stability problems of liposome can be resolved without influencing their intrinsic characteristics. Improvement of Solubility and bioavailability of poorly water soluble drugs.In the present work an attempt was being made to formulate and evaluate ganciclovir proliposomal gel for topical delivery for the treatment of viral infections. Phosphatidyl choline, Cholesterol and mannitol were used as excipients in the preparation of proliposomes. The drug and excipient compatibility was studied by using FTIR. The prepared proliposomes were tested for drug release F2 formulation shown maximum drug release which is considered as the optimized formulation. Gel formulation was prepared by taking different quantities of gellan gum. To the prepared gel formulations the optimized proliposomes were incorporated and then diffusion studies were conducted to the gel formulations to know the in vitro drug release. Formulation F2 shown maximum drug release hence it was considered as optimized formulation.

Keywords: *Ganciclovir, Proliposomal gel, Proliposomes, Liposomes, Excipients, liposomal dispersion.*

INTRODUCTION

Transdermal drug delivery systems (TDDS) are dosage forms involves drug transport to viable epidermal and or dermal tissues of the skin for local therapeutic effect while a very major fraction of drug is transported into the systemic circulation [1].

At present, the most common form of delivery of drugs is the oral route. While this has the notable advantage of easy administration, it also has significant drawbacks namely poor bioavailability due to hepatic metabolism (first pass) and the tendency to produce rapid blood level spikes leading to a need for high and/or frequent dosing, which can be both cost prohibitive and inconvenient.

To overcome these difficulties there is a need for the development of new drug delivery system; which will improve the therapeutic efficacy and safety of drugs by more precise (i.e., site specific), spatial and temporal placement within the body thereby reducing both size and number of doses. The success of transdermal delivery depends on the ability of the drug to permeate the skin in sufficient quantities to achieve its desired therapeutic effects. The skin is very effective as a selective penetration barrier [2].

Proliposomes

Proliposomes are defined as dry, free flowing powder formulations containing water soluble carrier particles coated with phospholipids that immediately form a liposomal dispersion on contact with water in the body. The resulting liposomes may act as a sustained release dosage form of the loaded drugs [3].

Proliposomes are composed of drug, phospholipid and a water soluble porous powder and can be stored sterilized in a dried state. Because of the solid properties, the

stability problems of liposome can be resolved without influencing their intrinsic characteristics.

Improvement of Solubility and bioavailability of poorly water soluble drugs [4].

Advantages of proliposomes over liposomes

- The stability problem of liposomes can be resolved Sterilization is easy.
- They immediately form liposomal suspension due to the presence of water soluble matrix (mannitol).
- For proliposomes to be used in cosmetics and skin care it is essential that they should have following properties.

I. Ability to be taken up in stratum corneum i.e., horny layer of epidermis.
II. Ability to penetrate the horny layer
III. Ability to exert an influence on the cellular metabolism of the living epidermis [5].

The mechanism involved in skin proliposomes interaction

It has been proposed that once inside the horny layer, proliposomes act in two different ways.

Firstly,proliposomal phospholipids (with high water binding capacity) are incorporated into the lipid lamellar of the lipid barrier causing reformation of flattened vesicular structures. Incorporation of phospholipids containing high proportion of unsaturated fatty acids reverses the physiological process of barrier formation and there is relative reduction in the quantity of the cholesterol (responsibility of rigidity) which results in beneficial increase in the fluidity of the lipid barrier. At the same Time, the high water binding capacity of phospholipids increases the degree of hydration of stratum corneum and reduces its roughness and at the same time making it possible for high molecular weight water soluble substances to permeate through lipid barrier. Penetration takes place through the gaps between the vesicular structures that are formed during interaction of liposomal phospholipids with the epidermal lipid barrier [6].

Secondly, vesicles function as the carriers of lipid or water soluble drug which by themselves are unable to enter the epidermis.

Proliposome could be prepared by many methods including crystal-film method, film-deposition on carriers method, fluidized-bed method, powder bed grinding method, freezing and drying method and spray drying method [7].

Proliposomes could be fabricated into various dosage forms including tablets/capsules, transdermal delivery systems, and those for vaginal administrations.

MATERIALS AND METHODS

Materials

Anciclovir provided by provided by chandra labs, hyderabad**,** mannitol, phosphatidyl choline, carbopol, chloroform, methanol, gellan gum and g cholesterol is obtained from sree srinivas private limited, hyd.

Preparation of proliposomal gel

The proliposomes containing Ganciclovir was prepared by film deposition on carrier method using vacuum rotary evaporator (Helidopath - Sonics-569-00050-00-0). There are various Process variables which could affect the preparation and properties of the proliposomes. The optimization of Ganciclovir proliposomes was done by preparing the different formulations by varying the concentration of mannitol, phosphatidyl choline and cholesterol Mannitol (1 g, sieved with 100 mesh) was placed in 100ml round bottom flask which was held at 60-70^{0}C temperature and the flask rotated at 80-90 rpm for 30 min under vacuum. After complete drying the temperature of waterbath was lowered to 20 [8].

Table 01: Composition of proliposomal formulations (F1 to F8)

Excipients	F1	F2	F3	F4	F5	F6	F7	F8
Ganciclovir (mg)	250	250	250	250	250	250	250	250
Mannitol(g)	1	1	1	1	1	1	1	1
Phosphatidyl choline(mg)	50	100	150	200	-	-	-	-
Cholesterol(mg)	-	-	-	-	50	100	150	200
Chloroform(ml)	8	8	8	8	8	8	8	8
Methanol (ml)	8	8	8	8	8	8	8	8

Preparation of Gellan gum gel base:

1gm of Gellan gum was weighed and dispersed in distilled water. Then, propylene glycol was added and the mixture was neutralised by drop wise addition of 1% triethanolamine. Mixing was continued until the transparent gel was obtained and allowed to swell for 24 hours. Similarly 2% and 3% Gellan gum gels were prepared [9].

Table 02: Composition of gel formulation

Formulation (F)	Gellan gum (mg)	Triethanolamine	Methanol (ml)	Diethyl ether (ml)	Water
F_1	100	1%	15	0.05	Q.s
F_2	200	1%	15	0.05	Q.s
F_3	300	1%	15	0.05	Q.s

Preparation of proliposomal gels:

Proliposomes containing Ganciclovir (separated from the unentrapped drug) were mixed into the 1% gellan gum gel by using mortar and pestle, the concentration of proliposomes in The gel being 1%. All optimized formulations were incorporated into different gels (1%,2% and 3%) [10].

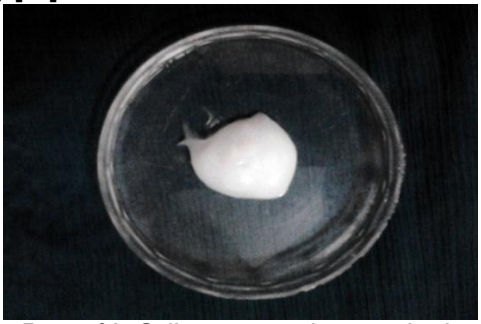


Figure 01: Gellan gum proliposomal gel

RESULTS & DISCUSSION

Preformulation studies

Melting point determination: Melting point of Ganciclovir was determined by capillary method. Melting point of Ganciclovir was found to be in the range of 152-155^{0}C which compiles the standards thus indicating that purity of the drug sample.

Construction of calibration curve using phosphate buffer (P^H 7.4)

Table 03: Standard calibration curve of drug in phosphate Buffer (PH 7.4)

S.No	Concentration	Absorbance
1	0.5	0.2251
2	1	0.4195
3	1.5	0.6407
4	2	0.8013
5	2.5	0.9971

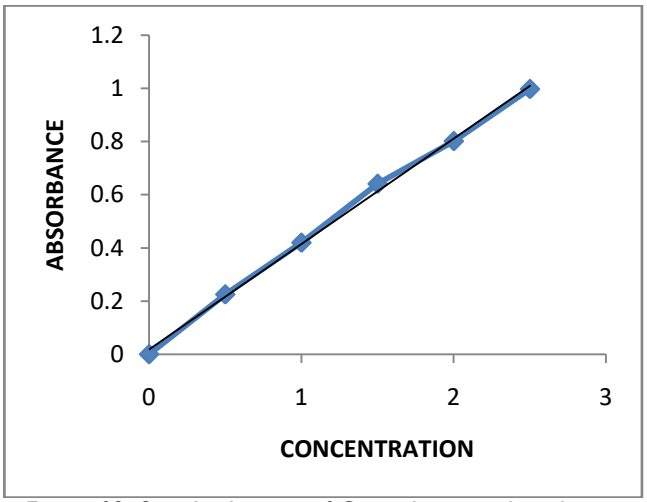


Figure 02: Standard curve of Ganciclovir in phosphate buffer (PH 7.4)

Drug- excipient compatibility studies using FTIR

On comparison of IR spectra of proliposomes, pure Ganciclovir drug, mannitol, cholesterol and phospholipid it was clear that, there was no significant interaction of encapsulated drug with the phospholipid and water soluble solid support (mannitol) with formulations [11-14].

i. Pure Drug

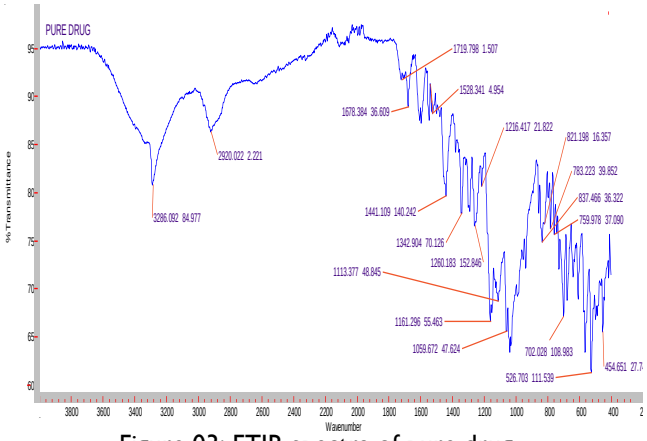


Figure 03: FTIR spectra of pure drug

ii. Optimized Formulation

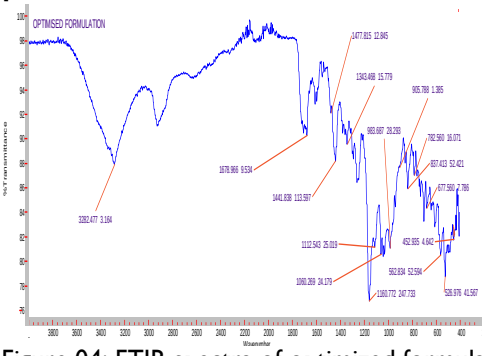


Figure 04: FTIR spectra of optimized formulation

CHARACTERIZATION PROLIPOSOMES AND PROLIPOSOMAL GELS

Determination of vesicle size

The most important parameter, which needs to monitor during proliposome preparation for its best performance, is the vesicle size and size distribution of liposomes. Several reports, showed the effect of liposome size on the drug release as well as drug deposition in the skin. A positive correlation was observed for both variables phospholipid and cholesterol in case of liposome vesicle size. Thus, with increase in the concentration of phospholipid and cholesterol vesicle size was found to be increased.Proliposomal sample was placed under digital microscope (Metzer, India) and hydrated with water. Then formation of vesicle was observed within the liposomal dispersion. Results of average vesicle size and distribution were calculated for count and distribution [16-20].

Table 04: Particle size of proliposomal formulations.

S.No	Formulation	Average particle size (µm) for 100 particles
1	F1	6.43
2	F2	5.86
3	F3	3.57
4	F4	5.62
5	F5	4.62
6	F6	5.87
7	F7	3.98
8	F8	3.01

Determination of entrapment efficiency

Determination of entrapment efficiency is an important parameter in case of liposomes as it majorly effects the drug release and skin deposition. Entrapment efficiency is expressed as the fraction of drug incorporated into liposomes relative to total amount of drug used [13].

Table 05: Entrapment efficiency of proliposome formulations

S.No	Formulation	Entrapment efficiency ± SD
1	F1	94.9±0.244
2	F2	85.12±1.48
3	F3	91.02±0.613
4	F4	96.5±0.205
5	F5	92.7±0.249
6	F6	94.1±0.509
7	F7	88.1±2.19
8	F8	89.2±0.817

A positive correlation was observed for both variables phospholipid and cholesterol. Results show that with increase in the concentration of phospholipid and cholesterol entrapment efficiency found to be increased. In the present study, the observed entrapment efficiency for all batches of Ganciclovir proliposome formulation in the range of 72 to 90%. Among all Ganciclovir proliposomal formulations F1-F8 had maximum vesicle size and entrapment efficiency which were selected for the further study [21-24].

Drug content estimation

Table 06: Drug content of proliposomal formulations

S.No	Formulation	%drug content ± SD
1	F1	96.7
2	F2	85.3
3	F3	92.6
4	F4	95.7
5	F5	92.4
6	F6	95.6
7	F7	93.7
8	F8	91.6

Percentage yield of proliposomes

Percentage yield for F1-F8 formulation was found to be with increase in the phospholipids concentration [25].

Table 7: Percentage yield of proliposomal formulations

S.No	Formulation	Percentage yield
1	F1	92.7
2	F2	91.9
3	F3	87.8
4	F4	93.5
5	F5	93.9
6	F6	95.2
7	F7	87.6
8	F8	88.5

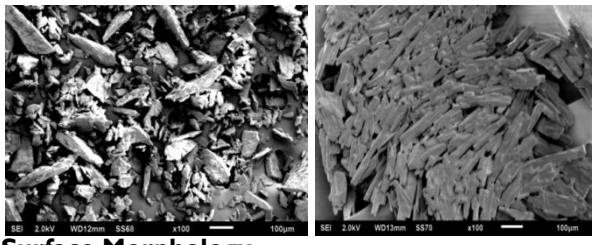
The % yield of formulations was found to be increase with increase in phospholipid concentration. The results of % yield of various formulations were found to be in the range of 86.5 ± 0.265 to 95.4 ± 0.221 (mean±SD, n=3) % as the drug to phospholipid ratio in proliposomes was changed [26-31].

Viscosity measurement

Rheological studies revealed that 1% Gellan gum gel showing better rheological properties when compared to 2% and 3% Gellan gum gels. So 1% Gellan gum was used for preparation of proliposomal gel. Viscosity of the gel was measured by Brookfield viscometer (LVDV II pro+). Viscosity of proliposomal gel showed 1156cps at 100rpm [32].

P^H measurement

The P^H of the developed formulation was in accordance with human skin P^H rendering them more acceptable. Therefore formulated proliposomal gel was suitable for topical application. The P^H values of prepared proliposomal gels were within the limits of 5.5 to 5.8 [33-3].



Surface Morphology

Figure 05: SEM image of Ganciclovir and Ganciclovir proliposomes

In – vitro studies [37]

The cumulative amount of drug release of various proliposomes formulations

Table 08: In-vitro drug release studies of different gel formulations

Time(hrs)	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
0.5	5.67	6.58	6.98	4.88	3.98	7.98	5.27	4.86
1	10.45	15.88	14.56	10.54	11.56	13.65	9.31	11.71
2	20.46	24.22	21.67	21.56	25.75	19.78	15.67	21.65
3	32.65	32.61	34.62	29.87	37.74	28.18	22.78	38.76
4	48.71	39.39	48.43	39.1	49.54	38.89	34.76	49.71
5	56.62	47.55	58.92	44.98	56.27	48.67	43.78	57.41
6	69.35	55.76	63.43	56.92	66.75	59.91	55.76	65.81
7	77.51	61.73	77.13	68.77	79.63	69.41	62.87	72.76
8	81.54	69.54	81.34	73.65	82.75	76.98	75.61	77.61
9	83.45	78.79	83.76	78.56	84.17	81.65	81.76	82.45
10	86.59	85.27	85.98	82.19	89.32	85.71	89.94	85.52
11	88.82	90.69	88.42	85.35	91.85	89.75	88.83	88.65
12	90.13	96.48	92.18	90.12	92.89	92.57	93.9	90.53

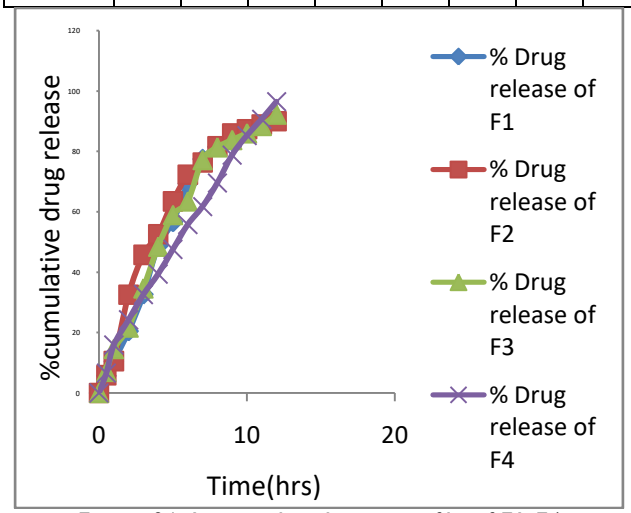


Figure 06: Invitro dissolution profile of F1-F4

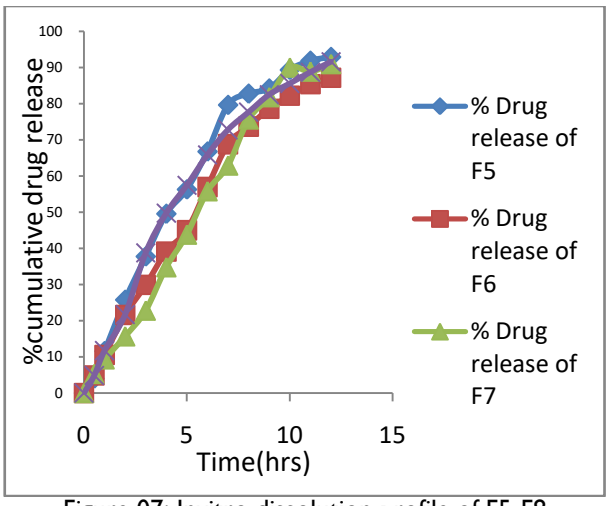


Figure 07: Invitro dissolution profile of F5-F8

Stability studies

Stability studies of optimized Proliposomes was performed at 80^{0}C, RT, and at 40^{0}C for three months and analysed for visual appearance, drug content and entrapment efficiency (table 12). After 3 months of storage period the ganciclovir Proliposomes still appeared free flow and immediately form a liposomal dispersion on contact with water. The results indicated that at elevated temperature and freezing temperature there was slightly but insignificantly decreases in drug content and entrapment efficiency for Proliposomes. So the proliposomal products should be stored in refrigeration conditions, to minimize the drug leakage from the proliposomal systems compared to conventional gel formulation [39].

Table 09: Stability studies results

Sl. No	Time (days)	Temperature(0C)	Drug content	Entrapment efficiency
1	15	RT	94.9	95.12
2	15	8	94.1	94.5
3	15	40	93.4	93.9
4	30	RT	92.9	93.1
5	30	8	92.1	92.7
6	30	40	91.8	92.1
7	60	RT	91.5	91.8
8	60	8	91	89.8
9	60	40	90.2	88.7

SUMMARY AND CONCLUSION

In the present work an attempt was being made to formulate and evaluate ganciclovir proliposomal gel for topical delivery for the treatment of viral infections. Phosphatidyl choline, Cholesterol and mannitol were used as excipients in the preparation of proliposomes. The drug and excipient compatibility was studied by using FTIR .The prepared proliposomes were tested for drug release F2 formulation shown maximum drug release which is considered as the optimized formulation. Gel formulation was prepared by taking different quantities of gellan gum .To the prepared gel formulations the optimized proliposomes were incorporated and then diffusion studies were conducted to the gel formulations to know the in vitro drug release. Formulation F2 shown maximum drug release hence it was considered as optimized formulation.

AUTHOR CONTRIBUTIONS

All authors contributed equally.

COMPETING INTEREST STATEMENT

No conflict of interests regarding publication of this paper.

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ETHICAL APPROVAL

Not applicable.

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