WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 10, Issue 10, 1282-1291. Research Article ISSN 2277– 7105

DEVELOPMENT AND CHARACTERIZATION OF EMULGEL FOR TOPICAL DELIVERY OF 5-FLUOROURACIL

Manisha Verma[1*], Dev Sharan Chaturvedi[2], Neha Chaturvedi[3], Jeetendra Kushwaha[4], Manish Kumar Sahu[5]

[1]Asst. Professor, Shanti College of Pharmacy Nowgong.
[2]Associate Professor, Shanti College of Pharmacy Nowgong.
[3]Associate Professor, SR College of Pharmaceutical Science Jhansi.
[4,5]Asst. Professor, Shanti College of Pharmacy Nowgong.

Article Received on
19 June 2021,
Revised on 09 July 2021,
Accepted on 30 July 2021
DOI: 10.20959/wjpr202110-21295

***Corresponding Author**
Manisha Verma
Asst. Professor, Shanti College of Pharmacy Nowgong.

ABSTRACT

Object: Aim of this study was development and characterization of emulgel for topical delivery of 5-FU. **Material & Method:** different concentration of carbapol 940 was used for prepration of different form of emulgel. **Result & Discussion:** According to solubility parameter 5-FU was soluble in distilled water. Partition coefficient value of 5-FU is {$P_{O/W}$ = 16.85 x 10^{-2} for n-Octanol/ water, 12.96x10^{-2} for n-Octanol/PBS (pH 7.4) and 10.57x10^{-2} for n-Octanol/PBS(pH7.6)}. Acidic solution of 5-FU was scanned in UV visible spectophotometric method was found to be reproducible and highly sensitive. Standard curve of 5-FU was obtained the straight line. Correlation coefficient was found to be greater than 0.99. According to invitro study the release of drug from its emulsified gel formulation can be ranked in following descending order $F_2 > F_1 > F_4 > F_3$. **Conclusion:** All the detail parameters proved that developed 5-FU loaded transfersomal gel improve the skin absorption of 5-FU and provide better treatment of skin cancer.

KEYWORDS: Emulgel, Carbapol 940, 5-Fluorouracil, Topical drug delivery.

INTRODUCTION

Skin cancer is the most common type of cancer affecting Caucasian populations. It has a very high rate of Cancer is the state that is characterized by spontaneous outgrowth of abnormal

mass of cells. The unpredictable microenvironment of the cancerous cells in all of its existing forms i.e. leukemic cells, solid tumors, and sarcomas is well documented.

This phenomenon expressed by cancerous sites in the body poses various obstacles towards drug's efficacy. Under normal conditions, the cells reproduce, grow, divide, multiply and eventually undergo apoptosis. This maintains proper balance and functioning of the organs. Cancer is caused in all instances either by mutation or by some other abnormal activation of cellular genes (oncogenes) that control cell growth and cell mitosis. As a consequence of mutations the normal cell is converted to oncogene and the genetic setup begins to develop in such a way so as to delay senescence.[1]

Topical delivery of drug

There has been increased interest during recent years in use of topical vehicle systems that could modify drug penetration into the skin. Optimal vehicles have to exert a high capacity for incorporating both lipophilic and hydrophilic drugs as well as high skin permeability. Many of the dermal vehicles contain chemical enhancers and strong solvents to achieve these goals (Walters, 1989). This is a major disadvantage, especially in chronic application, where they may usually be irritants. Therefore, it is undoubtedly desirable to develop a topical vehicle system, which does not necessitate chemical enhancers or alcohols to facilitate drug penetration into and through the skin.[2]

The best way to overcome the limitation of conventional drug delivery system is the use of different carrier systems like liposomes, niosomes, ethosomes, elastic liposome's, micro emulsion, solid lipid Nano particles and nanostructured lipid carrier or some alternate cost effective system like emulgel or organogel.[3]

Advantages of carrier approach for topical delivery of drugs

- Increase the skin permeation and deposition of drug
- Increase the drug bioavailability
- Minimizes the drug degradation and loss
- Sustained or continuous effect of medication
- Reduction in skin irritation potential

Vesicular Approaches for Topical Drug Delivery

The encapsulation of drug in lipid vesicles prepared from phospholipids and nonionic surfactant is used for transport of drug into and across the skin. The use of lipid vesicles as a topical drug carrier is justified below.[4]

- Vesicles can incorporate both hydrophilic and lipophilic drugs.
- Vesicles may serve as rate limiting membrane barrier for systemic absorption of drug.
- Because of the amphiphilic nature of the vesicles, these vesicles may serve as non-toxic penetration enhancer for drugs.
- Vesicles may serve as rate-limiting membrane barrier for systemic absorption of drug.
- They may serve as "organic solvent" for the solublization of poorly soluble drugs.

MATERIAL AND METHOD

Important Constituents of Emulgel Preparation

1. Aqueous Material: This forms the aqueous phase of the emulsion. Commonly used agents are water, alcohols.[5]

2. Oil: These agents form the oily phase if the emulsion. For externally applied emulsions, mineral oils, either alone or combined with soft or hard paraffins, are widely used both as the vehicle for the drug and for their occlusive and sensory characteristics.[6]

Table 1: Different type of oils to be used in dosage form. . In my project Liquid paraffin, Propylene glycol was used as a oil.

Chemicals	Quantity	Dosage form
Light Liquid Paraffin	7.5%	Emulsion and Emulgel
Isopropylmyristate	7-7.5%	Emulsion
Isopropyl stearate	7-7.5%	Emulsion
Isopropyl palmitate	7-7.5%	Emulsion
Propylene glycol	3.5%	Gel

3. Emulsifiers: Emulsifying agents are used both to promote emulsification at the time of manufacture and to control stability during a shelf life that can vary from days for extemporaneously prepared emulsions to months or years for commercial preparations.eg Polyethylene glycol 40.[7] stearate, Sorbitan mono- oleate.[8] (Span 80), Polyoxyethylene sorbitan monooleate (Tween 80).[9], Stearic acid[10], Sodium stearate.[11]

4. Gelling Agent: These are the agents used to increase the consistency of any dosage form can also be used as thickening agent.[12,13]

Table 2: Different gelling agents are used in Dosage Form. In my project carbopol-940 was used as a thickening agent.

Name	Quantity	Dosage form
Carbopol-934	1%	Emulgel
Carbopol-940	1%	Emulgel
HPMC-2910	2.5%	Emulgel
HPMC	3.5%	Gel
Gel sodium CMC	1%	Gel

5. Permeation Enhancers: These are agents that partition into and interact with skin constituents to induce a temporary and reversible increase in skin permeability.[14]

Table 3: Quantity of different Penitration enhancer agents used in dosage form. different type of penetration enhancer are used in emulgel formulation. In my project menthol was used as a penetration enhancer.

Name	Quantity	Dosage form
Oleic acid	1%	Gel
Lecithine	5%	Gel
Urea	10%	Gel
Isopropyl myristate	5%	Gel
Menthol	4-6%	Emulgel

Preparation of 5-FU formulation[15]

Different formulations were prepared using varying amount of gelling agent and penetration enhancers. The method only differed in process of making gel in different formulation.

Emulgel was prepared by dispersing Carbopol 940 in purified water with constant stirring at a moderate speed then the pH are adjusted to 6 to 6.5 using Tri ethanol amine (TEA). The oil phase of the emulsion were prepared by dissolving Span 20 in light liquid paraffin while the aqueous phase was prepared by dissolving Tween 20 in purified water32. Methyl and Propyl paraben was dissolved in propylene glycol whereas drug was dissolved in ethanol and both solutions were mixed with the aqueous phase. Both the oily and aqueous phases were separately heated to 70° to 80°C; then the oily phase were added to the aqueous phase with continuous stirring until cooled to room temperature. The obtained emulsion was mixed with the gel in 1:1 ratio with gentle stirring to obtain the emulgel. The composition of different formulations has been discussed in Table 4.

Table 4: Composition of different formulation batches (%w/w).

Ingredient	F1	F2	F3	F4
5-FU	1	1	1	1
Carbapol 940	1	1.25	1.5	1.75
Liquid paraffin	7.5	7.5	7.5	7.5
Tween 20	0.5	0.5	0.5	0.5
Span 20	1	1	1	1
Propylene glycol	5	5	5	5
Ethanol	2.5	2.5	2.5	2.5
Methyl parabene	0.03	0.03	0.03	0.03
Ethyl Parabene	0.01	0..01	0.01	0.01
Clove Oil	-	-	8	10
Mentha Oil	4	6	-	-
Water	q.s.	q.s.	q.s.	q.s.

RESULT AND DISCUSSION

5-FU was gifted from Biochem Pharmaceutical Industries Ltd-Daman and identified as per tests prescribed in Indian Pharmacopoeia (1996). An infrared spectrum of provided drug was found to be concordant with the reference infrared spectrum of the 5-FU given in Florey, (1973). Solubility study in different solvents at room temperature revealed that it is soluble in distilled water and insoluble in chloroform, benzene etc. Partition coefficient value of 5-FU also revealed its hydrophilic nature {$P_{O/W}$ = 16.85 x 10^{-2} for n-Octanol/ water, 12.96x10^{-2} for n-Octanol/PBS (pH 7.4) and 10.57x10^{-2} for n-Octanol/PBS(pH7.6)}.

An acidic solution of 5-FU was scanned in the U.V. range of 200-400 nm using Shimadzu 1800 UV Visible spectrophotometer as prescribed in I.P. 1996. The spectrophotometric method of analysis of 5-FU at λ_{max} 266.0 nm was found to be reproducible and highly sensitive.

The standard curves of 5-FU were prepared in PBS (pH 6.8) at λ_{max} 266.0 nm. The data were regressed to obtain the straight line.

The correlation coefficient greater than 0.99 was observed in all the cases, which indicated that, the drug follows Beer-Lambert's law in the concentration range of 2-20 μg/ml. In the present study,

Polymers were selected on the basis of their solubility's and non-interference in the estimation of drug.

The absorbance data of both drug and different additives were noted. The absorbance data had shown no appreciable change in the absorbance of drug solon at 266.0 nm indicating no interference of polymers in the estimation of 5- FU.

1. Physical appearance: Emulgel formulations were yellowish white viscous creamy preparation with a smooth homogeneous texture and glossy appearance. Results have been discussed in table 5.

Table 5: Physical parameters of formulation batches.

Formulation	Color	Homogeneity	Consistency	Phase separation
F1	White	Excellent	Excellent	None
F2	White	Excellent	Excellent	None
F3	Pale Yellow	Excellent	Excellent	None
F4	Yellow	Excellent	Excellent	None

2. Morphological appearance (Optical microscopy): Emulgel formulation were yellowish white viscous creamy preparation with smooth homogeneous texture and glossy appearance. Results have been discussed in table 6.

Table 6: Physical parameters of formulation batches.

Formulation	Color	Homogeneity	Consistency	Phase separation
F1	White	Excellent	Excellent	None
F2	White	Excellent	Excellent	None
F3	Pale Yellow	Excellent	Excellent	None
F4	Yellow	Excellent	Excellent	None

3. Spreading coefficient: The spreading coefficient of various gels formulations are given below in table 7.

Table 7: Spreading coefficient of formulation batches.

Formulation	Spreading Coefficient(g.cm/sec)
F1	13
F2	14
F3	10.5
F4	10

4. Rheological studies: The tests were performed at 100 rpm for 10 min. Results are given in table 8.

Table 8: Rheological studies of the formulation.

Formulation	Viscosity (centipoises)
F1	1300
F2	1400
F3	790
F4	800

5. Bioadhesive strength measurement: The bioadhesive strength of various emulgel formulations have been shown below in table 9.

Table 9: Bioadhesive strength of the formulation.

Formulation	Adhesion Strength (kg/cm^2)
F1	4.3
F2	5
F3	3.8
F4	3.2

6. In-vitro drug release study: The study showed the release of the drugs from its emulsified gel formulation can be ranked in the following descending order: F2 > F1 > F4> F3 where the amounts of the drug release of the drug released after 240 min were 56.01%, 53.48%, 52.23%, 51.21%, respectively.

Table 10: Data for in-vitro cumulative % drug release data of formulations.

Time (min)	F1	F2	F3	F4
0	0.00	0.00	0.00	0.00
5	11.02	14.55	11.82	08.90
10	14.92	15.76	14.54	12.20
15	20.43	18.24	16.44	14.78
20	29.04	25.75	32.74	24.70
30	40.95	41.84	42.14	38.10
60	42.56	48.04	44.64	44.60
120	47.37	53.74	47.44	50.00
240	53.48	56.01	51.25	52.23

7. Drug content: Drug content details of emulgel are shown in table no.11.

Table 11: percent drug content of the formulation.

Formulation	Percent Drug Content
F1	91 %
F2	95%
F3	84%
F4	78%

Optimization of Formulation: From the result formulation F2 and F1 show maximum drug release, drug entrapment, spredablity, viscosity and biodhesive strength. So these formulations were selected for further study.

8. Stability Studies: Stability study was performed on optimized batches F_2 and F_4 at ambient conditions. The results obtained after 1 month time period are shown in table 12.

Table 12: Stability studies of the optimized formulations.

Before					
F2			F1		
Appearance	pH	Drug content	Appearance	pH	Drug content
White	6.5	95%	Yellowish	6.5	91%

After					
F2			F1		
Appearance	pH	Drug content	Appearance	pH	Drug content
White	6.4	95%	Yellow	6.4	91%

CONCLUSION

As the emulgel is recent technique for topical drug delivery it is better suitable for hydrophobic drugs and it is very good technique for drug delivery of combination of both hydrophilic and hydrophobic drugs. Since emulgel had appear as a new and novel technique for topical drug delivery. mainly the hydrophobic drug formulation can be developed with emulgel technique on the other hand hydrogel are not suitable for hydrophobic drugs.

5-fluorouracil (5-Fu) is an antineoplastic drug, topically used for the treatment of actinic keratosis and nonmelanoma skin cancer. It is shows poor percutaneous permeation by the conventionally applicable creams and thus inefficient for the treatment of deep-seated skin cancer. In the present article, emulgel containing 5-Fu was investigated for the treatment of skin cancer. Different formulation of emulgel was prepared using Tween-20 and Span-20 as edge activators. The vesicles were characterized for Shape, particle size, percentage entrapment efficiency, deformability and In- Vitro skin permiation. Optimized formulation was incorporated into carbopol 940 gel and evaluated for efficacy in the treatment of skin cancer.

We concluded that the developed 5-Fu-loaded transfersomal gel improves the skin absorption of 5-Fu and provide a better treatment for skin cancerapplications. In addition, low-dose 5-Fu

appeared to have good general tolerability and was well accepted by both physicians and patients in terms of clinical and cosmetic outcomes.

In the coming years, topical drug delivery will be used for extensively to impart better patient compliance. Since emulgel is helpful in enhancing spreadability, adhesion, viscosity and extrusion, this novel drug delivery become popular, more ever they will become a solution for loading hydrophobic drugs in water soluble gel base for the long term stability.

Topical emulgels of 5-Fu were formulated and characteized to physicochemical studies *i.e.* rheological studies, spreading coefficient studies and extrudability test, in vitro release studies. In vitro release of the tests formulations were performed to determine drug release rate from emulgel and drug release was found from formulation F2 and F1 56.01% and 53.48% in 4 h respectively percentage drug content of the formulations were performed to determine durg content from formulation and drug content was found F2 and F1 95% and 91%. The formulations F1 and F2 were comparable with marketed topical gel. So 5-fluorouracil emulgel can be used as an anti-cancer agent for topical drug delivery.

ACKNOWLEDGEMENT

According to the history of all great work was done by the active or passive support of a person.

I am highly thankful to my respected sir Dev Sharan Chaturvedi sir for his active guidance throughout the completion of research paper.

REFERENCES

1. Kitson, N.; Thewalt, J.L. Acta. Derm. Venerol, 2000; 208: 12-5.
2. Brigger I., Dubernet C., Couvreur P. , Nanoparticles in cancer therapy and diagnosis, Adv Drug Deliv Rev, 2002; 13: 631-51.
3. Didov M. G., Kumbaradzi E. F., Goracinova K., Calis S, Simonoska M, Hincal A, 5-Fluorouracil in topical liposome gels for anticancer treatment Formulation and evaluation, Acta Pharm, 2003; 53: 241–250.
4. Schreier H and Bouwstra J, Liposomes and niosomes as topical drug carriers — dermal and transdermal drug-delivery. J Control Rel, *1994;* 30: 1-15. 83.
5. Singh PB. Choudhary PK, Penetration enhancers for transfer drug delivery of systemic agents, J Pharm Res, 2007; 6: 44-50.

6. Gaur PK, Mishra S, Purohit S, Dave K. Transdermal Drug Delivery System: A Review. AJPCR, 2009; 2: 14-20.
7. Lachman, L.; Lieberman, H.A. The Theory and Practice of Industrial Pharmacy. 3rd Ed. Varghese Publishing house, 1990; 534.
8. Vyas, S.P.; Khar, R.K. Controlled Drug Delivery. 1st Ed. Vallabh Prakashan, 2002; 416-417.
9. Bonacucina G, Cespi M, Palmieri GF. Characterization and Stability of Emulsion Gels Based on Acrylamide/Sodium Acryloyldimethyl Taurate Copolymer AAPS Pharm Sci Tech. June 2009; 10 (2).
10. Curr AEB. Transdermal Drug Delivery: Penetration Enhancement Techniques Heather. Drug Deliv, 2005; 2: 23-33.
11. Rutrer N. Drug absorption through the skin: a mixed blessing .Arch Dis Child, 1987; 62: 220-221.
12. Zhang XL, Zhao R, Qian W. Preparation of an emulgel for treatment of aphthous ulcer on the basis of carbomers. Chin. Pharm. J, 1995; 30: 417-418.
13. Swarbrick, J. Encyclopedia of pharmaceutical technology, 3rd ed, 1551.
14. Gibson, M. Pharmaceutical formulation and preformulation, Interpharm, 2004.
15. Mortazavi SA, Aboofazeli R. An Investigation into the Effect of Various Penetration Enhancers on Percutaneous Absorption of Piroxicam. Iranian Journal of Pharmaceutical Research, 2003; 135-140.