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ARTÍCULO ORIGINAL

Comparative Investigation on *in vitro* release of extemporaneously prepared norfloxacin semisolid formulations with marketed silver sulfadiazine 1% cream, USP using model independent approach

Dua K[1]*, Pabreja K[2], Ramana MV[3]

[1]*Lecturer, Dept. of Pharmaceutical Technology, School of Pharmacy & Allied Health Sciences, International Medical University, Bukit Jalil, Malaysia
[2]Lecturer, Dept. of Life Sciences, School of Pharmacy & Allied Health Sciences, International Medical University, Bukit Jalil, Malaysia.
[3]Professor, VIT University, Vellore, Tamilnadu, India.
kamalpharmacist@gmail.com

ABSTRACT

Objective

In an attempt for better treatment of bacterial infections, various semisolid formulations containing 5% w/w of norfloxacin were prepared and evaluated for *in vitro* drug release and *in vitro* skin permeability using dialysis membrane and rat abdominal skin respectively. The *in vitro* diffusion and permeation profile of the prepared formulation was compared with marketed silver sulfadiazine cream 1%, USP using model independent approach.

Methods

Various semisolid formulations were prepared with different dermatological bases using standard procedures. *In vitro* diffusion and permeation studies were carried out using Keshary-Chein (KC) type diffusion cell using dialysis membrane and rat abdominal skin respectively.

Results

The f_1 lower than 15 and f_2 higher than 50 indicated similarities in the *in vitro* diffusion and permeation profiles of the extemporaneously prepared selected semisolid formulations and marketed silver sulfadiazine 1% cream, USP.

Conclusion

Amongst all the semisolid formulations prepared, carbopol gel base was found to be most suitable dermatological base for norfloxacin, the results obtained for in vitro diffusion, and *in vitro* skin permeation studies are comparable with that of marketed silver sulphadiazine 1% cream, USP.

KEYWORDS: Semisolid, Ointments, Norfloxacin

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1. INTRODUCTION

Topical antibiotics can play an important role in prevention and treatment of many primary cutaneous bacterial infections commonly seen in dermatological practice like localized superficial infections due to surgery, injury and abrasion. Topical antimicrobials help in preventing entry of microorganism into wound, which leads to fast healing of wounds. Quinolones belongs to synthetic class of antimicrobial agents with potent antimicrobial activity which are effective orally and parentally for a wide variety of infectious diseases[2] .

Norfloxacin, a broad-spectrum fluroquinolone antibacterial agent, is commonly employed in the treatment of urinary and genital tract infections[3]. It is a hydrophilic fluroquinolone with unique physiochemical properties such as low water solubility and partition coefficient[4, 5]. The objective of the present study was to prepare various topical drug delivery systems such as gels and ointments and to evaluate and compare *in vitro* diffusion and permeation profile of the prepared formulation with marketed silver sulfadiazine cream 1%, USP using model independent approach.

2. MATERIAL AND METHODS

Norfloxacin (Pfiscar India Ltd., Murthal, India); Carbopol (Noveon, Mumbai, India). All other chemicals used were of analytical grade, UV- Spectrophotometer (Jasco V-530, Jasco Inc., 8649, Commerce Dr., Easton, MD-21601).

2.1 Preparation of semisolid dosage forms of Norfloxacin

Various semisolid formulations of norfloxacin (NF) were prepared according to the composition given in Table-1 with different dermatological bases using standard procedures. In each of the formulations, NF was incorporated at 5% w/w concentration respectively in the base with trituration using geometric dilution procedure to obtain homogeneous mass.

Table 1: Composition of topical formulations of norfloxacin.

Ingredients↓	*Quantity in mg*								
	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
NF	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0
Sodium CMC		5.0							
Cetostearyl alcohol					15			15.0	
Yellow Beeswax					2.5	5.0		1.0	2.0
Carbopol 940	2.0								
Triethanolamine	q.s.								
Tween 80					5.5				
Borax						0.2			
Methyl paraben	0.15	0.2	0.3		0.2	0.2		0.2	
Propyl paraben	0.05	0.1	0.2		0.1	0.1	10.5	0.1	
Sodium metabisulphite								0.1	
SLS								2.0	
Hard Paraffin						7.0			
HPMC			2.0						
PEG 4000				50.0					
PEG 300				45.0					
DMSO							10.5		
Isopropyl myristate							8.0		
Mineral oil						45.0	30.5		
White petrolatum						10.0	30.7		83.0
Propylene glycol								10	
Span 60					7.5				
Wool fat									10.0
Bees wax							4.8		
Glycerine		24.0	10						
Water q.s	100	100	100		100	100		66.6	

CMC: carboxymethyl cellulose; DMSO: dimethyl sulfoxide; HPMC: hydroxylpropylmethyl cellulose; NF: norfloxacin; NFL: norfloxacin lactate; PEG: polyethylene glycol; SLS: sodium lauryl sulfate.

F_1- Carbopol gel base F_2- Sodium CMC gel F_3- HPMC gel

F_4- Macrogol gel F_5- Water miscible base F_6- Cold cream

F_7- Simple ointment base F_8- Beller's ointment base F_9- Oleagenous base

2.2 *In vitro* diffusion studies

In vitro diffusion studies for all formulations were carried out using Keshary-Chein (KC) type diffusion cell [6, 7]. The diffusion cell apparatus was fabricated locally as open-ended cylindrical tube with 3.7994cm^2 area and 100mm height having a diffusion area of 3.8cm^2. 1% v/v acetic acid was used as receptor media. The dialysis membrane (25cm^2) was soaked in water for a while, and then for 2h in isotonic phosphate buffer (IPB) solution, pH 7.4 (100ml) prior to be mounted on the diffusion cell. A weighed quantity of formulation equivalent to 25mg of drug was taken on to the dialysis membrane and was immersed slightly in 20ml of receptor medium, which was continuously stirred. The entire system was maintained at 37±1ºC. An aliquot of 2ml were withdrawn at specific time intervals up to 6 h, suitably diluted and the NF content was estimated spectrophotometrically at 277.6 nm. After each

withdrawal, the diffusion medium was replaced with an equal volume of fresh diffusion medium. Average of three determinations was used to calculate the cumulative percent drug release at each time interval[8, 9].

2.3 *In vitro* skin permeability studies

In vitro skin permeation studies were carried out for the best three formulations, which exhibited the higher drug release through dialysis membrane using Keshary-Chein (KC) diffusion cell [6, 7] in a similar way as described for *In vitro* diffusion studies using rat abdominal skin. The rat skin was obtained from the abdominal portion of albino rat after sacrificing the animal. The hair and fat were removed after treating the skin with 0.32 mol L^{-1} ammonia solution for 30 minutes[10] . The skin was tied to the KC diffusion cell (donor cell) such that the stratum corneum side of the skin was in intimate contact with the release surface of the formulation in the donor cell[11]. All experiments were carried out in triplicate.

2.4 Comparison of *in vitro* diffusion and *in vitro* permeation profiles

The *in vitro diffusion* and *in vitro* skin permeation profiles of the best among the three selected formulations in each case was compared for similarity with marketed silver sulfadiazine 1% cream, USP. A Model-Independent Approach was used employing a difference factor (f_1,) and similarity factor (f_2) as given in equations 1 and 2, respectively[12, 13].

(1) $$f_1 = \frac{\sum[R_t - T_t]}{\sum R_t} \times 100$$

(2) $$f_2 = 50 \cdot \mathrm{Log}\left[\frac{1}{\sqrt{1 + \frac{1}{n}\sum (R_t - T_t)^2}} \times 100\right]$$

Where, R_t and T_t are % dissolved for reference and test formulation at each time point and n is the number of time points in dissolution profile. The time intervals used to study the f_1 and f_2 were up to 420 min.

The f_1 value increase proportionally due to the dissimilarity between the two release profiles. If f_1 value lies between 0-15 and f_2 value of two drug release profiles is between 50 and 100, then these two drug profiles are considered similar. Value under 50 indicates difference between the release profiles. The value of f_2 = 50 reflects 10% difference; when

value is >50, the difference between R and T is less than 10% [14].

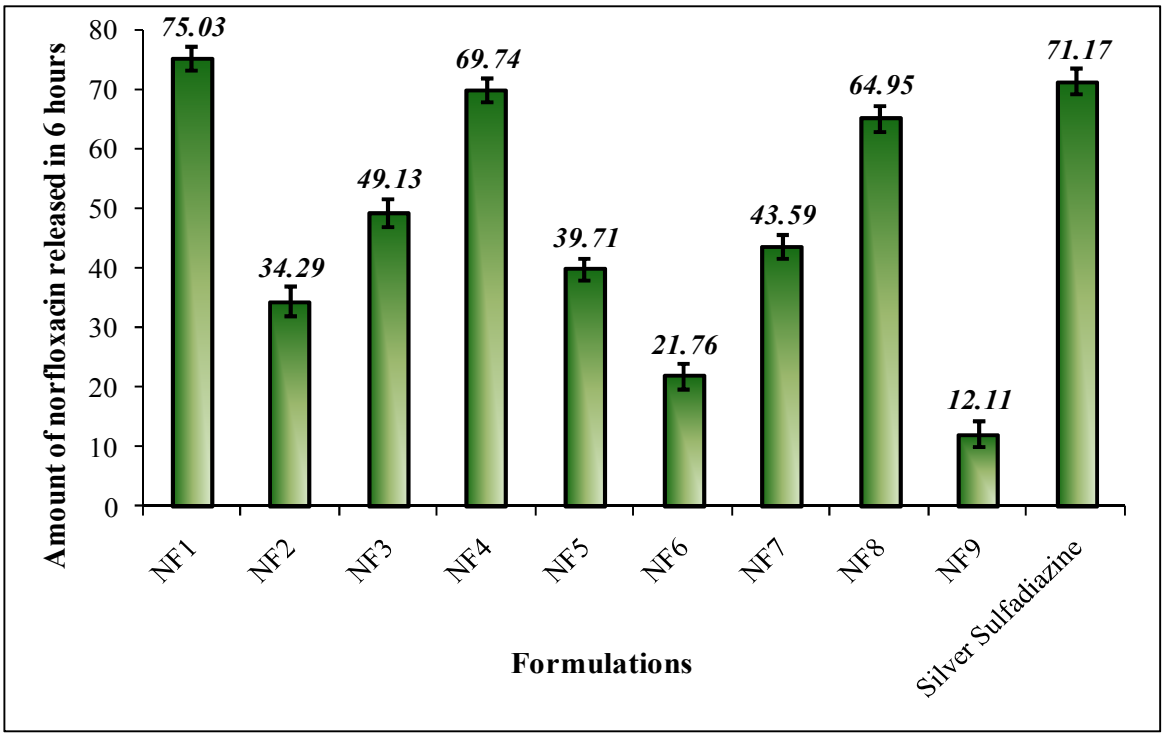
3. RESULTS AND DISCUSSION

3.1 *In vitro* diffusion and skin permeability studies

In the present investigation, *in vitro* diffusion and permeation were found to be better for Carbopol gel formulations (NF_1) in comparison to the formulations containing various other dermatological bases. The effect of dermatological bases on drug release profiles has been well documented[15, 16]. The following cumulative amount of drug diffusion for NF_1 at 6 h was observed to be 75.03±1.96% and the cumulative amount of drug permeation at the same time interval was 16.16±0.75%.

The comparative release of NF from various formulations is shown in Figure 1. The enhanced drug diffusion and drug permeation from the Carbopol gel base may be attributed to the presence of pores in the gel which allow relatively free diffusion of the drug to the vehicle and lack of over-solubilization of the lipophilic drug in the aqueous vehicle and hence readily available for release[17] .In creams and various oleaginous bases, owing to their biphasic nature, partitioning of the drug occurs in aqueous and oil phases which results in the slower release of drug. In case of gels, the drug diffusion occurs through the aqueous phase and hence they offer a greater drug diffusion and release.

Figure 1: Comparative *in vitro diffusion* of different norfloxacin semisolid formulations with marketed silver sulfadiazine 1% cream, USP in 6h.



The results obtained for *in vitro* diffusion and *in vitro* skin permeation studies with NF are comparable with that of silver sulphadiazine 1% cream, USP (SS: 71.17±2.10%; 15.95±0.68% respectively for *in vitro* diffusion and skin permeation) available in market.

The extent of *in vitro* permeation of drug through skin after 6h was observed to be in the range 12.88±0.63 to 16.16±0.75. The extent of permeation of the drug is not sufficient to exert a systemic action but it is sufficient to exert a local action at the site of application. This inadequate permeation through the skin is possibly due to a strong affinity of hydrophobic drug to the lipophilic stratum corneum or the barrier effect of the latter despite using permeation enhancers. However, the diffusion of NF from the three selected formulations was in the same order as that from dialysis membrane.

3.2 Comparison of *in vitro diffusion* and *in vitro* permeation profiles

The Comparative *in vitro* diffusion and *in vitro* skin permeation of selected norfloxacin semisolid formulations with marketed silver sulfadiazine 1% cream, at 6 h is shown in Figure 2. The values of f_1 and f_2 for the NF_1 as compared to that of the marketed silver sulfadiazine 1% cream, USP, were given in Table 2 and Figure 3 and 4. The f_1 lower than 15 and f_2 higher than 50 indicated similarities in the *in vitro* diffusion and permeation profiles. Thus, the data indicate that the release mechanism of the drug from all the formulation follows the same pattern.

Figure 2: Comparative *in vitro* diffusion and *in vitro* skin permeation of selected norfloxacin semisolid formulations with marketed silver sulfadiazine 1% cream, at 6 h.

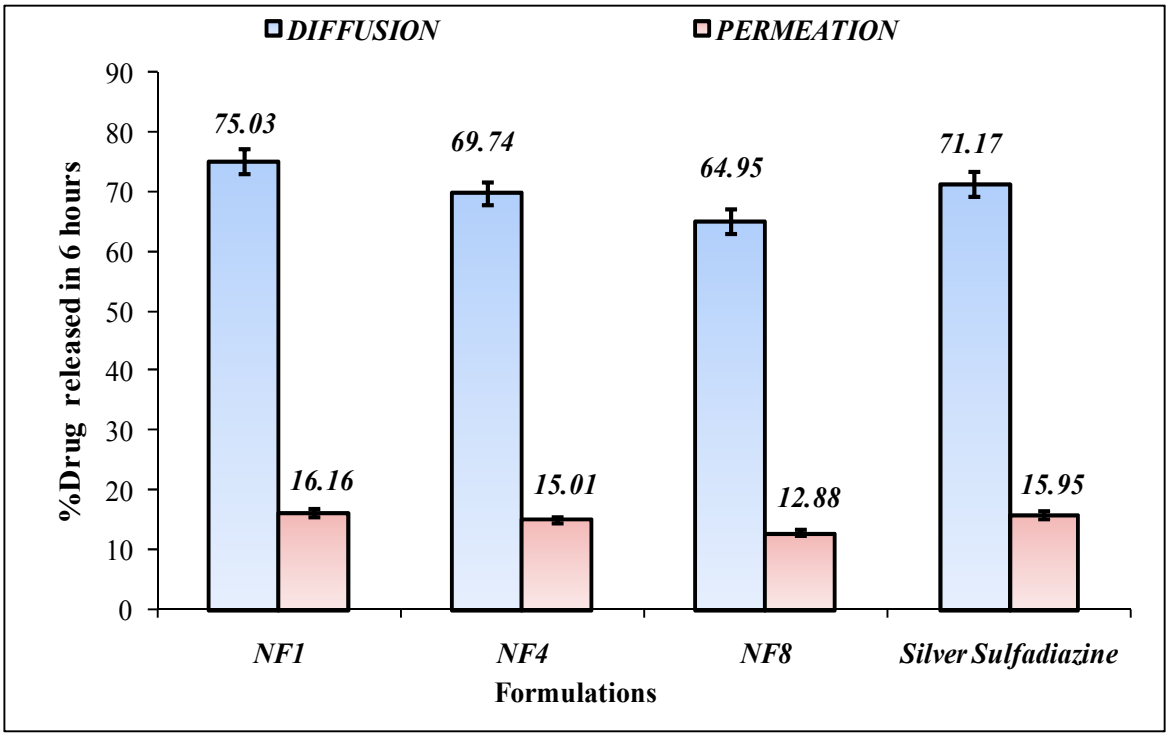


Table 2. Analysis of f_1 (difference factor) and f_2 (similarity factor) value of NF_1 and NFL_1 with marketed silver sulfadiazine 1% cream, USP.

Formulation	*Drug release study*	f_1	f_2
NF_1	***In vitro* diffusion**	5.82	71.03
	***In vitro* skin permeation**	9.77	90.51

Figure 3: Analysis of *in vitro* diffusion profile for f_1 (difference factor) and f_2 (similarity factor) of NF_1 with marketed silver sulfadiazine 1% cream, USP.

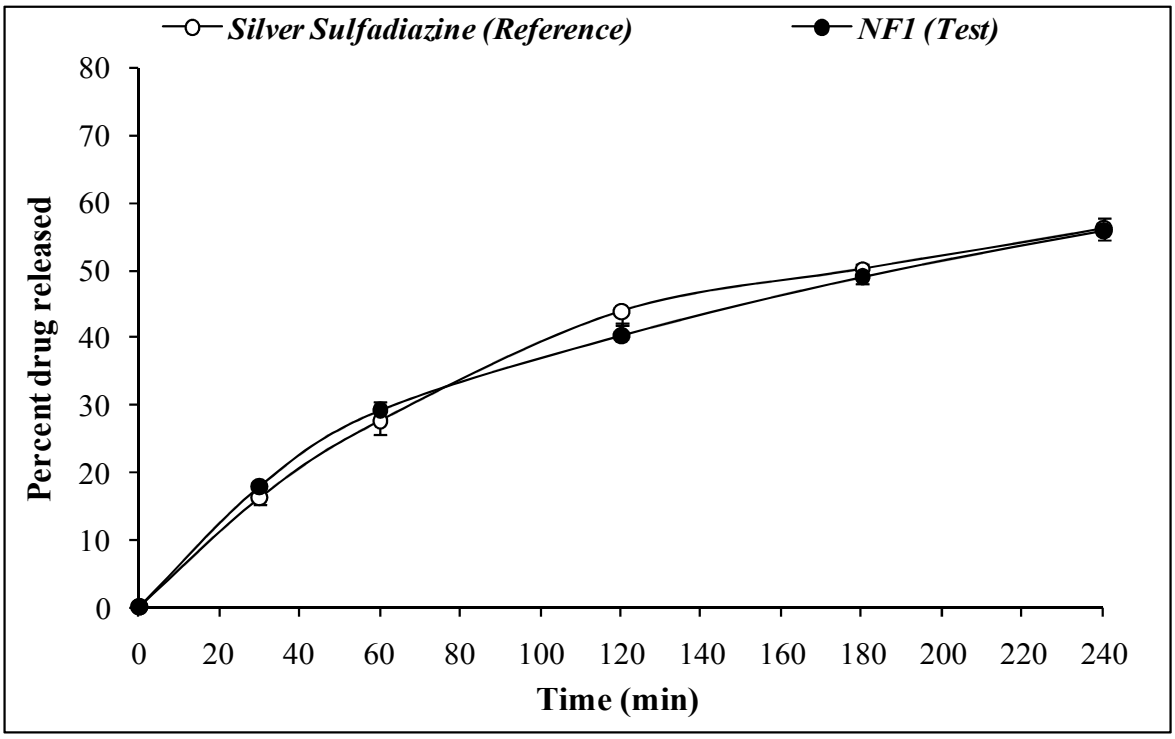
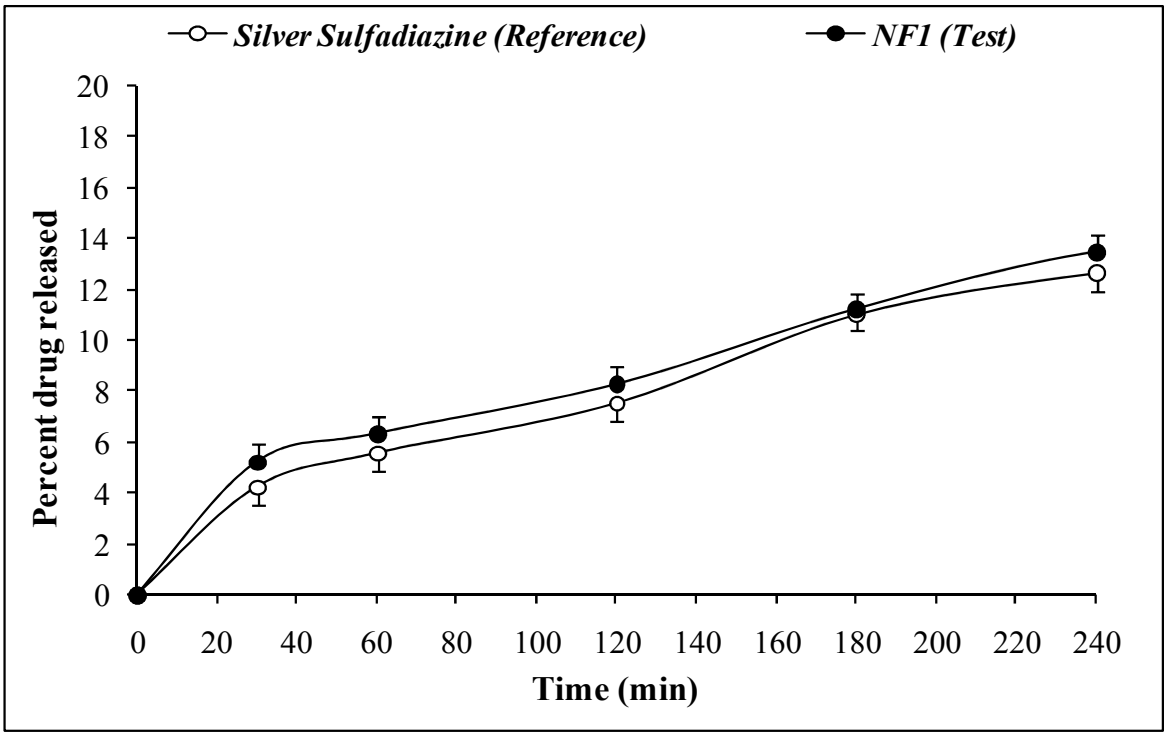


Figure 4: Analysis of *in vitro* skin permeation profile for f_1 (difference factor) and f_2 (similarity factor) of NF_1 with marketed silver sulfadiazine 1% cream, USP.



4. CONCLUSION

The *in vitro* release characteristics of the prepared topical formulations of norfloxacin were quite encouraging and in agreement with marketed Silver Sulfadiazine 1% Cream, USP. Amongst all the semisolid formulations prepared, Carbopol gel base was found to be most suitable dermatological base for norfloxacin in comparison to various other dermatological bases. It also has aesthetic appeal, which other bases lack, an important aspect from patient compliance and consumer point of view.

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