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Design, Formulation and Evaluation of Topical Nimesulide Emulgel

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Abstract : Emulgel is one of the recent technologies in Novel DDS used for dual control release of emulsion and gel for topical use. In the present Investigation, topical gel and emulgels of Nimesulide were formulated using 2^3 Factorial Design and Carboplol 934 as a polymer.The oral use of Nimesulide is associated with side effects like gastrointestinal disturbances, epigastric pain, nausea, heartburn, vomiting and diarrhea. Topical application of the drug prevents these side effects and offers potential advantage of delivering the drug at the site of action. The rational of the present study was to increase the penetration of drug into the skin.The Formulations were subjected to various physicochemical studies such as spreading coefficnt, Vioscosity and in vitro release studies. In vitro release of the tests formulations was performed to determine drug release from Gel and emulgel. From the in vitro studies, formulation F4 showed maximum release of 59.58% in 240 min and 45.02% from the Gel. In vitro release studies of the prepared formulation were performed using dialysis membrane and results indicated that Emulgel showed better release than Gel system.
Keywords : Emulgel, Topical Drug delivery, Nimesulide, Drug release kinetics.

Introduction:

Transdermal drug delivery is a convenient approach for the treatment of many skin related disorders.Topical drug delivery is a localized drug delivery system used for the therapeutic effect at the site of their application acting into the underlying layers of skin or mucous membranes.[1]

Gels are prepared by entrapment of large amounts of aqueous liquid within a colloidal solid particles network, which may consist of inorganic substances. When compared with the ointment or cream, gels have a higher aqueous component that permits greater dissolution and migration of the active ingredients apart from several advantages as, thixotropic, greaseless, easily spreadable, easily removable and emollient in nature. [2]Emulsions (O/W & W/O) are used mainly as vehicles in transdermal drug delivery system and have advantage of elegance and are easily washable. [3]

When combined form of gels and emulsions are used in a dosage forms they are referred as, emulgels.[4]Emulgels with advantage of both gels and emulsion act as a controlled drug delivery system for

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topically applied drugs. They are emulsion of either oil in water type or water in oil type which are gelled by mixing with a gelling agent. [5]The emulgel allows the addition of hydrophobic drugs in the oil phase which leads to the dispersion of oil globules in aqueous phase resulting in formation of o/w [6]

Many conventional used ointment, creams, lotions have several disadvantages. They are sticky in nature causing uneasiness to the patient, have lesser spreading coefficient so applied by rubbing and they exibit the problem of stability.So to overcome this limitations an emulsion based Gel approach could be used to incorporate hydrophobic drug moiety. [7]

Nimesulide is a second generation non–steroidal anti– inflammatory agent, which is widely used in the long-term therapy of rheumatoid arthritis and inflammation. Its biological half–life reported to be 3 to 4 hrs. [8] The oral use of Nimesulide is associated with side effects like gastrointestinal disturbances, epigastric pain, nausea, heartburn, vomiting and diarrhoea. Topical application of the drug prevents these side effects and offers potential advantage of delivering the drug at the site of action [9]

It is important to design an optimized formulation of Emulgel with a desired drug release rate and minimum number of trials. Many statistical experimental designs have been recognized as useful techniques to optimize the process variables. 2-level factorial design utilizing a polynomial equation has been widely used which requires minimum experimentation and time, thus is far more effective and cost-effective than the conventional methods of formulating emulgel. In the present study an attempt was made to investigate transdermal delivery of Nimesulide from emulgel formulation using 2^3 factorial design.

Experimental:

Materials

Nimesulide was procured from Dr. Reddy's laboratories, Hyderabad.,Carbopol 934 was obtained from Hi Media laboratories Pvt. Ltd. Triethanolamine was procured from Qualigens fine chemicals. All other chemicals were used of analytical grade and without any further chemical modification

Method:

Preparation of Gel

The Gel was prepared by dispersing Carbopol 934 in purified water with constant stirring using mechanical stirer at a moderate speed then the pH is adjusted to 6 to 6.5 using Triethanolamine (TEA) [10]

Table 1: Formulation of Gel: -

Sr.no	Ingredients	Quantity taken
1	Carbopol 934	1 gm
2	Tri - ethanolamine	q.s
3	Drug (Nimeculide)	1 gm
4	Distilled Water	Upto 100ml

3 Preparation of Emulgel :

Emulgel of Nimesulide was prepared by using 2^3Factorial design. Different formulations were prepared using varying amount of gelling agent. The preparation of emulsion was same in all the formulations. The Gel in formulations were prepared by dispersing Carbopol 934 in purified water with constant stirring at a moderate speed then pH is adjusted to 6 to 6.5 using Tri Ethanol Amine (TEA). The oil phase of the emulsion was prepared by dissolving Span 80 in light liquid paraffin while the aqueous phase was prepared by dissolving Tween 20 in purified water. Methyl paraben was dissolved in propylene glycol where Nimesulide was dissolved in water and both solutions was mixed with aqueous phase. Both the oily and aqueous phases were separately heated to 70 to 80 C; then the aqueous phase were added to the oil phase with continuous stirring until cooled to room temperature using homogenizer. Then mixing of gel and emulsion in ratio 1:1 to obtain the emulgel [11]Total Eight Batches were prepared and composition of different formulations are shown in Table2 and 3.

A 2^3 factorial design was conducted to statistically optimize the formulation factors and to study the effect of independent variables , Concentration of Carbopol (X1) tween 20(X2) and Span80 (X3) on dependent variables % cumulative drug release (Y1) and spreading coefficient (Y2) using Design Expert software (StatEase Inc., Minneapolis, MN)

Table 2: 2^3FactoralDesign

Carbopol	Tween	Span
-1 (0.5)	-1 (0.5)	-1 (0.5)
1 (1)	-1 (0.5)	-1 (0.5)
-1 (0.5)	1 (1)	-1 (0.5)
1 (1)	1 (1)	-1 (0.5)
-1 (0.5)	-1 (0.5)	1 (1)
1 (1)	-1 (0.5)	1 (1)
-1 (0.5)	1 (1)	1 (1)
1 (1)	1 (1)	1 (1)

Table 3: Formulation of Emulgel:

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
Nimesulide	1	1	1	1	1	1	1	1
Carbopol 934	0.5	1	0.5	1	0.5	1	0.5	1
Span 80	0.5	0.5	0.5	0.5	1	1	1	1
Liquid paraffin	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
Tween 20	0.5	0.5	1	1	0.5	0.5	1	1
Methyl paraben	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
PEG 400	5	5	5	5	5	5	5	5

Evaluation of Emulgel:

Melting Point Determination

Melting point of Nimesulide was determined by using open capillary tube method. [13]

Physical appearance

The prepared Emulgel formulations were inspected visually for their pH, colour, homogeneity, consistency, grittiness and phase separation. [14]

Determination of pH

The pH values of 1% aqueous solutions of the emulgels were measured by a pH meter.[15]

Viscosity measurement

The viscosity of the different emulgel formulations was determined at $25^{O}C$ using Brookfield viscometer equipped with spindle number 64, and the viscosities were recorded at different rotational speeds of 10, 20, 50, and 100 RPM. [16]

Spreadability

The Spreadability of the formulation was determined by an apparatus suggested by [17]which was suitably modified in the laboratory and used for the study. It consist of a wooden block, which was provided by a pulley at one end. A rectangular ground glass plate was fixed on this block. An excess of gel (about 1 g) under the study was placed on this ground plate. The gel was then sandwiched between this plate and another glass plate having the dimension of fixed ground plate and provided with the hook. A 1 kg weight was placed

on the top of two plates for 5 minutes to expel air and to provide a uniform film of the gel between the plates. Excess of gel was scrapped off from the edges. The top plate was then subjected to pull of 10g. with the help of string attached to the hook and the time (second) required by the top plate to cover a distance of 5 cm was noted .[18]

Drug content studies

Accurately weighed 1 g of gel was transferred into 100 ml volumetric flask the volume was made up to 100 ml with phosphate buffer (pH 7.4).Then pipette out 1ml & dilute it upto 10ml. After suitable dilution the absorbance was measured using Shimadzu 1700 UV Visible spectrophotometer at 396nm.

In vitro diffusion studies:

In-vitro diffusion study was carried out in a Modified Franz diffusion cell. Emulgel (1 g) was evenly applied onto the surface of dialysis membrane. The dialysis membrane was clamped between the donor and the receptor chamber of diffusion cell filled pH 7.4 phosphate buffer. e receptor chamber was stirred by magnetic stirrer .The study was carried out at 37± 0.5 ºC and 100 rpm [19]. Samples were withdrawn from the sampling port of reservoir compartment at regular intervals and absorbance was measured using Shimadzu 1700 UV visible spectrophotometer at 396.5nm.

Drug release Kinetics:

Drug release kinetic

The release data obtained were treated according to zero-order, first-order, Higuchi and Korsmeyer-Peppas equation models.[20]

Results and Discussion:

Melting point determination:

The melting point was determined using capillary method and it was found to be 143^0C. [18]

Physical characterization

Emulgels were white viscous creamy preparation with a smooth homogeneous appearance and characteristic odor.

Determination of pH

pH values of all prepared formulation ranged from 6.0 to 6.9, which are considered acceptable to avoid the risk of irritation upon application to the skin because adult skin pH is 5.5.

Viscosity measurement

Rheological properties of the emulgels indicated that the systems were shear thinning in nature showing decrease in viscosity at the increasing shear rates. The viscosity of all the batches are shown in Table4. The results showed that, as concentration of Carbopol increases, viscosity of the emulgel found to be increased.[20]

Spreadability

This is One of the important criteria for an Emulgel is that it should possess good spreadability. Spreadability is a term expressed to denote the extent of area on which the gel readily spreads on application to the skin [21].The spreadability of various formulation from F1-G1 was mentioned in table 4.It shows that the F7 formulation shows higher spreading coefficient as compared to other formulations.

Drug content:

Table 4: Evaluation of Nimesulide Emulgel & Gel :

F. code	pH	Spreadability (gm.cm/sec)	(%) Drug Content	Viscocity (50rpm) (64)	
				%	CPS
F 1	4.74 ± 0.96	1.875 ± 1.04	95.97%	43.4	5200
F 2	4.38 ± 0.36	1.667 ± 1.34	100.12%	95.5	11400
F 3	4.65 ± 0.16	2.084 ± 1.06	99.02%	45.5	5464
F 4	4.00 ± 0.75	1.785 ± 1.09	98.53%	92.6	11140
F 5	4.76 ± 0.15	2.343 ± 1.26	95.97%	63.2	7610
F 6	4.30 ± 0.19	1.875± 1.35	94.59%	96.7	11660
F 7	4.75 ± 0.53	2.500± 1.08	99.30%	42.3	5050
F 8	4.22 ± 0.18	1.785± 1.09	90.98%	98.2	11800
G 1	3.74 ± 0.18	2.272± 1.18	99.86%	97.9	11740

***In- vitro* dissolution study**

In – vitro dissolution studies of different formulation F1-F8 of Nimesulide Emulgel and Nimesulide gel was carried out and the release data are shown in figure 1,2 and 3

The drug release from different batches was observed to be depend on the both the concentration of surfactant and polymer. [22] F4 batch show maximum drug release up to 59.584% after 240min and F1 batch show lowest drug release of 37.984% after 240min , the release of batch G1 is lower as compare to optimized batch of Emulgel . In general, it can be observed from the result that all emulgels showed better release as compared to Gel formulation.

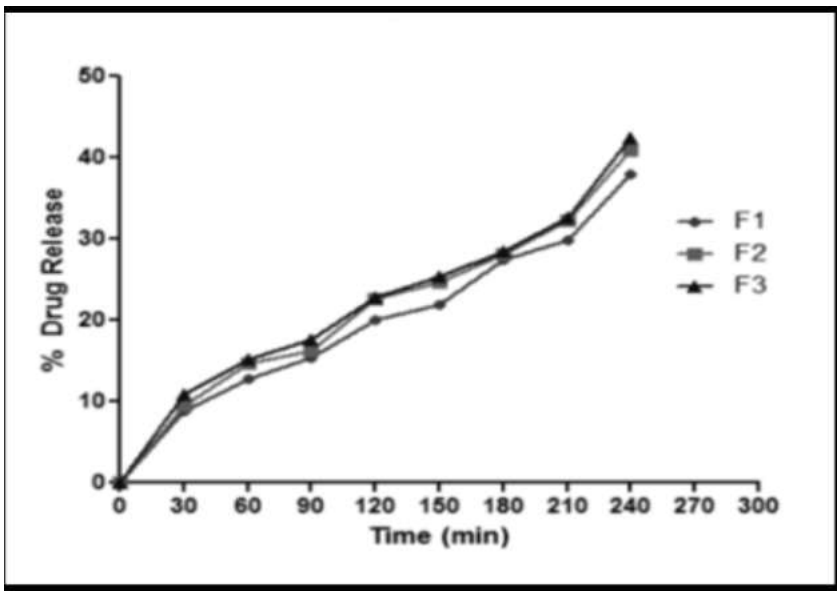

Fig 1: % drug release of batch F1-F3

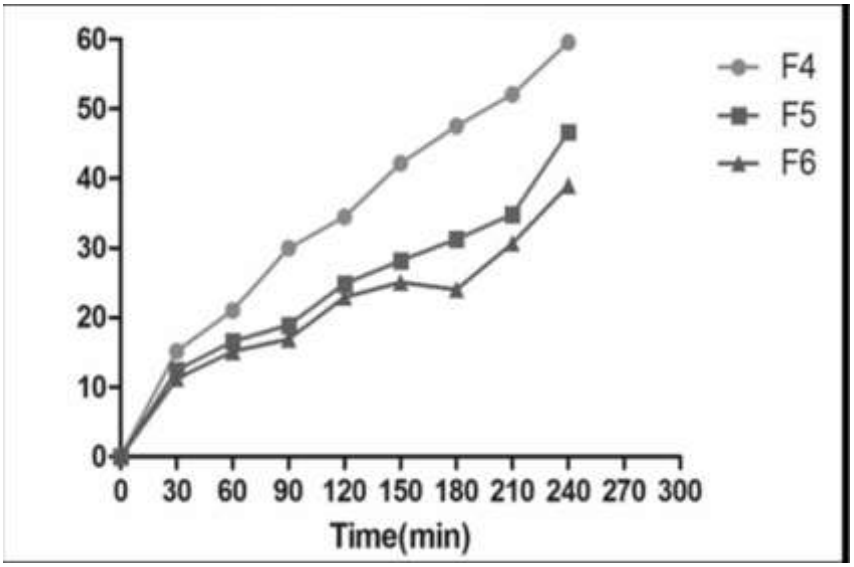

Fig 2: % drug release of batch F4-F6

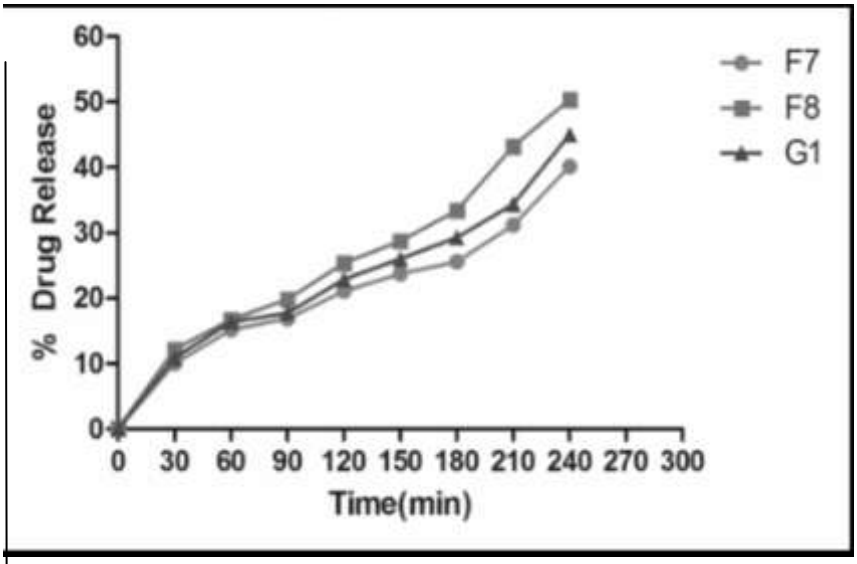

Fig 3: % drug release of batch F7,F8 and G1

Fig :-3 In – Vitro release of Nimeculide Emulgel & GeL

Drug release Kinetics:

The dissolution kinetics of batches from F1 to G1 was applied to various dissolution models such as Zero order, First order, Higuchi, Korsemayer-Peppas and Hixon-Crowell. The best fitted model gives the highest R2 value and least slope value given in table 5. The best fitting model for all the formulation was calculated. The batchs F1,F2,F3,F4,F5,F6 and F7 were found to be Korsmeyer- Peppasrelease. The only F8 batch show Hix. Crow release.

The value of n as estimated by linear regression of $\log(M_\infty/M_t)$ vs $\log(t)$ of formulation indicate a non-Fickian release behavior, which is indicative of drug release mechanisms involving a combination of both diffusion and chain relaxation mechanisms.

Table:5:- Drug release kinetic studies

Batch No.	Zero order		1st order		Matrix		Hix.Crow		Korsmeyer -Peppas		
	R	K	R	k	R	K	R	K	R	n	K
G1	0.9673	0.1789	0.9704	-0.0022	0.9553	2.3256	0.9718	-0.0007	0.9750	0.6264	1.2028
F1	0.9798	0.1550	0.9845	-0.0018	0.9597	2.0108	0.9843	-0.0006	0.9854	0.6739	0.8198
F2	0.9746	01673	0.9812	-0.0020	0.9628	2.1747	0.9808	-0.0006	0.9854	0.6650	0.9298
F3	0.9653	0.1717	0.9739	-0.0021	0.9641	2.2383	0.9731	-0.0006	0.9801	0.6134	1.2403
F4	0.9726	0.2651	0.9953	-0.0037	0.9814	3.4633	0.9921	-0.0011	0.9957	0.6661	1.4851
F5	0.9608	0.1876	0.9686	-0.0023	0.9618	2.4462	0.9688	-0.0007	0.9729	0.5941	1.4914
F6	0.9375	0.1602	0.9546	-0.0019	0.9655	2.1008	0.9502	-0.0006	0.9662	0.5502	1.6039
F7	0.9597	0.1611	0.9680	-0.0019	0.9607	2.1015	0.9671	-0.0006	0.9767	0.6040	1.2212
F8	0.9802	0.2053	0.9780	-0.0026	0.9498	2.6575	0.9815	-0.0008	0.9746	0.6647	1.1273

All the Formulations showed n value in the range of 0.5-1, which indicate Non-fickian release mechanism. Thus, the release of the drug from the prepared emulgel and gel is fast by swelling of polymer, followed by diffusion through the swelled polymer, fast erosion of the polymer.

5. Conclusion

Emulgel is one of the recent technologies in Novel DDS used for dual control release of emulsion and gel for topical use. Topical drug delivery generally used to impart better patient compliance. Emulgel is found to be helpful in enhancing spreadability, adhesion, viscosity and hence, this novel drug delivery becomes popular. Moreover, they will become a solution for loading hydrophobic drugs in water soluble gel bases for the long term stability. The stability of emulsion is increased, when it is incorporated into gel. The rational of the present study was to increase the penetration of drug into the skin. In the present Investigation, topical emulgels of Nimesulide were formulated and subjected to various physicochemical studies such as spreading coefficient, Viscosity and in vitro release studies. In vitro release of the tests formulations were performed to determine drug release from Gel and emulgel. From the in vitro studies, formulation F4 showed maximum release of 59.58% in 240 min and 45.02% from the Gel. So Nimesulide Emulgel can be used as an anti-inflammatory analgesic agent for topical drug delivery.

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