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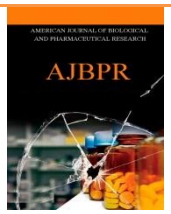

FORMULATION AND EVALUATION OF CELECOXIB EMULGEL FOR TOPICAL DELIVERY

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ABSTRACT

The use of non-steroidal anti-inflammatory drugs is well recognized for regional inflammatory disorders such as muscle pain, osteoarthritis, and rheumatoid arthritis. Celecoxib, a specific COX2 inhibitor, is one of the most potent non-steroidal anti-inflammatory agents. It is an insoluble drug and has irritant effect effect on GIT lead to ulceration and bleeding. The formulation of the product may play a key role for penetration and absorption of the active ingredient. Several formulation approaches for cutaneous administration of NSAIDS have been employed. The pharmaceutical forms particularly used for dermal administration to achieve local effects are gels, creams, ointments and emulgels. In the present study the emulgel was used for NSAIDs topical application. The aim of this study was to overcoming these two problems through preparation of this drug as topical emulgel. Sodium alginate and carbopol were the two polymers used as gelling agents, the influence of type and concentration of them on the release of celecoxib was investigated.

INTRODUCTION

Topical drug administration is a localized drug delivery system anywhere in the body through ophthalmic, rectal, vaginal and skin as topical routes. These are applying a wide spectrum of preparations for both cosmetic and dermatological, to their healthy or diseased skin. These formulations range in physicochemical nature from solid through semisolid to liquid. Topical drug must be of low molecular mass (600 dalton) with adequate solubility in oil and water, and have high partition coefficient for the topical formulation [1]. The main advantage of topical delivery system are to bypass first pass metabolism. Major drawback of topical dosage form is dissolution and diffusion of drug in the delivery of hydrophobic drugs.

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Therefore to overcome this limitation, emulgel are prepared [2]. The combined dosage form of gels and emulsion are reffered as emulgel. In fact, the presence of a gelling agent in the waterphase converts a classical emulsion into an emulgel. Both oil in water and water in oil emulsions are extensively used as vehicles to deliver various hydrophilic as well as hydrophobic drugs to the skin in emulgel formulation. They also have a high ability to dissolve drug and to penetrate the skin.

The celecoxib is a Non-steroidal anti-inflammatory drugs (NSAIDS) are among the most frequently prescribed drug groups. These drugs are used in the treatment of various rheumatic disease, including rheumatoid arthritis. The mechanism of action of NSAIDS is reversible inhibition of the cycloxygenase enzyme (COX) and decreasing the synthesis of prostaglandins. The acidic character of NSAIDs may lead to local irritation and lesions on the gastrointestinal mucosa. Therefore some NSAIDS are administered percutaneously and

transdermally to achieve local or systemic effect as an alternative to oral and parentral administration. Emulgel for dermatological use have several favorable properties such as being thixotropic greaseless, easily spreadable, emollient, non-staining ,water soluble, longer shelf life, -biofriendly, transparent and pleasing appearance [3].

In recent years ,there has been great attention in the use of novel polymers with complex functions as emulsifiers and thickners because the gelling agent capacity of these compounds allows the formulation of stable emulsions and creams by decreasing surface and interfacial tension and at the same time increasing the viscosity of the aqueous phase.H ence the aim of the work was to develop and characterize an emulgel formulation of celecoxib using carbopol and sodium alginate as gelling agent and penetration enhancer propylene glycol [4].

MATERIALS & METHODS

Drugs & Chemicals

Celecoxib, carbopol-940,sodium alginate was procured from Yarrow chemical product. All other chemicals used were analytical grade and used without any further chemical modification.

Pre formulation study

Before the development of any formulation, it is mandatory to carryout preformulation studies to findout any changes in the drug characreristics and stability of a drug [5].

Physical appearance

Physical appearance of drug was observed and compared with the pharmacopeial specification.

Melting point

Melting point of the drug was determined using specific melting point apparatus.

Solubility

Solubility of celecoxib was studied in different medium such as 0.1N HCL, 0.1N NaOH, acetone, methanol and water.

FORMULATION OF EMULGEL

Preparation Of Carbopol Gel

50 g of carbopol gel was prepared by dissolving 1.0g of carbopol powder in 49ml of purified water with aid of moderate speed stirrer(50 rpm) and then the ph was adjusted to 6-6.5 using triethanolamine.

Preparation of sodium alginate gel

50 g of sodium alginate gel was prepared by dispensing 3.5g of sodium alginate powder in 46.5 ml of heated purified water(80^0c). The dispersion was cooled to room temperature and left overnight to ensure hydration of gel and the ph was adjusted.

Preparation of emulsion

The oil phase was prepared by dissolving different amount of span 80 in liquid paraffin while the aqueous phase was prepared by dissolving the required amount of tween 20 in purified water.1g of celecoxib powder was dissolved in 25ml of methanol while 0.03g of methyl paraben and 0.01g of propyl paraben were dissolved in 5ml of propylene glycol and both were mixed with aqueous phase. Both aqueous and oily phase were separately heated 70-80^0c. Then oil phase was added to the aqueous phase with continuous stirring at 50 rpm until cooled to room temperature.

Preparation of emulgel

The emulsion was poured into gel (1:1 ratio) with gentle stirring until homogeneous emulgel was obtained [6]. The composition for the preparation of emulgel is given in table 1.

EVALUATION OF EMULGEL

Physical examination

The prepared emulgel formulations were inspected visually for their colour, homogeneity, consistency and phase separation [7].

pH of emulgel

The Ph of gel was determined by a digital Ph meter.1g of gel was dissolved in 25 ml of distilled water and the electrode was then dipped into the gel formulation and constant reading was noted [8, 9].

Drug content determination

Drug content study was done to determine the amount of the drug present in the certain quantity of the formulation. Briefly 1 g of the formulation into 10 ml volumetric flask added 1 ml methanol in it and shake well and make up the volume with PBS pH 7.4. The Volumetric flask was kept for 2 hr and shaken well in a shaker to mix it properly. The solution was passed through the filter paper and filtered the mixer then measured the absorbance by using spectrophotometer at 260 nm.

Drug Content = (Conc. × Dilution Factor × Vol. taken) × Conversion factor

Extrudability

The prepared emulgel formulations were filled in clean, lacquered aluminum collapsible tubes with a 5 mm opening nasal tip. Extrudability was then determined by measuring the amount of gel extruded through the tip when a constant load of 1 kg was placed over the pan. The extrudability of prepared Emulgel was calculated by using following formula.

Extrudability = Amount of gel extruded from the

tube/Total amount of gel filled in the tube *100.

***In-vitro* Drug release study**

The *in vitro* drug release studies of the Emulgel were carried out on Diffusion cell using egg membrane. This was clamped carefully to one end of the hollow glass tube of dialysis cell. Emulgel (1gm) was applied on to the surface of egg membrane dialysis to solubilize the drug. The receptor chamber was stirred by magnetic stirrer. The samples (1ml aliquots) were collected at suitable time interval and analyzed for drug content by UV visible spectrophotometer at 260 nm after appropriate dilutions. Cumulative corrections were made to obtain the total amount of drug release at each time interval. The cumulative amount of drug release across the egg membrane was determined as a function of time and calculated using standard calibration curve [8].

Details of dissolution testing

- Dissolution media: Phosphate buffer saline pH 7.4
- Speed: 50 rpm
- Aliquots taken at each time interval: 1 ml
- Temperature: 37±20C
- Wavelength: 260 nm

Stability study

The prepared emulgel was packed in aluminium collapsible tube (5g) and subjected to stability studies were carried out at 40^0 C (hot) 35 ^{0}C (normal),5 ^{0}C(cool).Samples were withdrawn at 1 month time interval up evaluated for physical appearance, pH drug content.

RESULTS AND DISUSSSION

Physical appearance

Physical appearance of the celecoxib was observed and the colour was found to be white.

Melting point

The melting point of celecoxib was found to be 188^0c.

Solubility

Solubility of celecoxib was studied quantitatively in different media such as 0.1 N HCl, 0. 1NaOH, acetone, methanol and water. The results are shown in the table no:2

Evaluation of emulgel

Physical examination

The prepared emulgel formulations were inspected visually for their colour,homogeneity,consistency,and phase separation and is given in the table no:3

pH of emulgel

The pH values of 1%aqueous solutions of the prepared Gellified emulsions were measured by pH meter and the result is shown in the given table. From this result all formulations having satisfied pH as that of references.

Drug content determination

Concentration of drug content was measured by spectrophotometer.It was measured by sonication. Absorbance was measured after suitable dilution in UV/VIS spectrophotometer.

The result is shown in the given table and the formulaton F3 shows the high drug content.

Extrudability

The method adopted for evaluating emulgel formulation for extrudability is based upon the quantity of emulgel and emulgel extruded from lacquered aluminium collapsible tube on application of 1 kg weight. More quantity extruded better is extrudability. The values are shown in the given table. The high value of extrudability for F3 formulation.

Invitro drug release

Fig no:7 shows the results of in vitro release of celecoxib. It appears that the F3 and F4 enhanced the release of celecoxib when compared the other formulation and the percentage of celecoxib released after 150 minutes from these formulations was 86% and 82% respectivel, while folmulae F2, F6 decreased extent of celecoxib released.

Stability study

The formulations were subjected at 3 different temperatures for 3 months to check the stability. There were no significant changes in their physical appearance. The samples were analysed for drug content at different time interval, and it was evident that there were slight changes in the content of the drug as shown in table no:8.

Table 1. Formulation table of emulgel

Formulation no	Celecoxib	Carbopol	Sodium alginate	Methanol	Liquid paraffin	Span80	Propylene glycol	Methyl paraben	Propyl Paraben	Tween80	Purified water
F1	1	1	-	2.5	6	1.5	5	0.03	0.01	0.95	100
F2	1	1	-	2.5	8	1.5	5	0.03	0.01	0.95	100
F3	1	1	-	2.5	6	2.5	5	0.03	0.01	1.25	100
F4	1	1	-	2.5	8	2.5	5	0.03	0.01	1.25	100

F5	1	-	3.5	2.5	6	1.5	5	0.03	0.01	0.95	100
F6	1	-	3.5	2.5	8	1.5	5	0.03	0.01	0.95	100
F7	1	-	3.5	2.5	6	2.5	5	0.03	0.01	1.25	100
F8	1	-	3.5	2.5	8	2.5	5	0.03	0.01	1.25	100

Table 2. Solubility of celecoxib

Medium	Solublity
0.1 N HCl	Insoluble
0.1N NaOH	Partially soluble
Acetone	Partially soluble
Methanol	Soluble
Water	Partially soluble

Table 3. Physical examination of celecoxib emulgel.

	F1	F2	F3	F4	F5	F6	F7	F8
Colour	White	White	White	White	White	White	White	White
Homogeneity	Good	Good	Good	Good	Good	Good	Good	Good
Consistency	Good	Good	Good	Good	Good	Good	Good	Good
Phase separation	No	No	No	No	No	No	No	No

Table 4. pH of emulgel.

	Carbopol				Sodium alginate			
Formulation code	F1	F2	F3	F4	F5	F6	F7	F8
Ph	6.76	6.59	6.8	6.66	6.7	6.58	6.79	6.6

Table 5. Drug content of celecoxib emulgel

Formulation code	Drug content(%)
F1	89.50
F2	82.05
F3	94.81
F4	84.32
F5	87.87
F6	80.29
F7	90.33
F8	83.68

Table 6. Extrudability of celecoxib emulgel

Sl.no	Formulation code	Weight extruded from tube(g)
1	F1	0.83
2	F2	0.90
3	F3	0.95
4	F4	0.530
5	F5	0.82
6	F6	0.62
7	F7	0.93
8	F8	0.92

Table 7. Invitro drug release study of celecoxib emulgel.

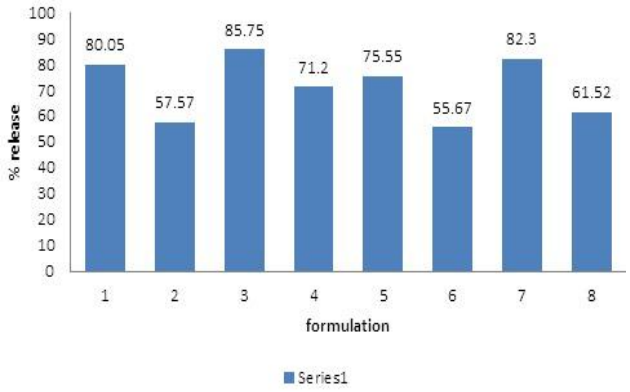
	Carbopol				Sodium alginate			
Time	1	2	3	4	1	2	3	4
0	38.28	15.10	42.75	27.33	29.35	9.46	32.40	18.92
30	43.11	18.92	50.60	34.18	37.84	14.75	45.32	22.87
60	56.73	22.87	65.40	41.20	44.78	18.56	58.12	37.80

90	61.55	31.20	72.75	56.42	55.08	29.99	64.40	45.32
120	72.10	43.37	80.14	65.80	63.42	40.54	79.22	50.47
150	80.05	57.57	85.75	71.20	75.55	55.67	82.30	61.52

Table 8. stability study of emulgel

Sl no	Formulation code	Month	appearance	Ph	Drug content
1	F1	0 day	White	6.76	89.50
		30 day	White	6.76	89.50
		60 day	White	6.64	89.48
		90 day	White	6.58	89.45
2	F2	0 day	White	6.59	82.05
		30 day	White	6.58	82.05
		60 day	White	6.41	81.98
		90 day	White	6.32	81.96
3	F3	0 day	White	6.80	94.81
		30 day	White	6.80	94.81
		60 day	White	6.78	94.79
		90 day	White	6.76	94.78
4	F4	0 day	White	6.66	84.32
		30 day	White	6.66	84.32
		60 day	White	6.49	84.27
		90 day	White	6.35	84.24
5	F5	0 day	White	6.70	87.87
		30 day	White	6.70	87.87
		60 day	White	6.58	87.84
		90 day	White	6.49	87.82
6	F6	0 day	White	6.58	80.29
		30 day	White	6.57	80.29
		60 day	White	6.40	79.99
		90 day	White	6.31	79.90
7	F7	0 day	White	6.79	90.33
		30 day	White	6.79	90.33
		60 day	White	6.68	90.28
		90 day	White	6.65	90.26
8	F8	0 day	White	6.60	83.68
		30 day	White	6.60	83.68
		60 day	White	6.54	83.65
		90 day	White	6.47	83.60

Fig 1. Cumulative % release of celecoxib emulgel.



CONCLUSION

Formulation of celecoxib emulgel was developed successfully using different polymers like carbopol and sodium alginate.the characterization of each polymer and drug were carried out.

The formulated emulgel were evaluated and the drug release pattern was studied. The pH, consistency, homogenicity of the emulgels was checked and the evaluation gives satisfactory values.the drug release pattern of all the formulations were done using franz-diffusin cell. the result showed that the formulation containing carbopol as gelling agent give good release compared with sodium alginate. The low concentration of liquid paraffin gave good release pattern compared with the higher one. The stability study shows that all formulations are stable during the study period.

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