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Influence of different gelling polymers on dexibuprofen gel formulation: *In- vitro* characterization and stability profile

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Abstract: The present study was designed to formulate a 5% topical gel formulation containing dexibuprofen. Herein, we reported the utilization of different gelling polymers including hydroxyl propyl methyl cellulose (HPMC), carboxy methyl cellulose (CMC), carbopol 940 and leutrol F127 at three concentration levels. Overall, twelve trials (TD1 to TD12) were prepared in four batches (DEX-I to DEX-IV), each having three trial dexibuprofen gel formulations. All formulations were evaluated for organoleptic properties, clarity, pH, consistency, viscosity and spreadability. Trials of DEX-I and DEX- III batches (containing HPMC and carbopol 940polymers respectively), were a lack in smoothness, clarity and viscosity. Contra wise, TD5, TD6 dexibuprofen gel formulations of batch DEX-II and TD10, TD11 and TD12 of DEX-IV having CMC and lutrol® F127 correspondingly were found to be viscous and free from grittiness and precipitation. *In vitro* drug kinetics revealed the Weibull kinetic model as the best (r^2>0.999, AIC 31.427-37.381, MSC 2.259-3.421). Stability testing was performed on the selected formulations (TD5, TD6, TD10, TD11 and TD12) having acceptable physicochemical attributes. Only TD11 and TD12 were found to be stable at room temperature after three months. Based on the findings, it is concluded that lutrol® F127 based dexibuprofen gel formulations delivered excellent spreadability, better drug release, and satisfactory stability profile.

Keywords: Dexibuprofen, lutrol® F127, HPMC, carbopol, CMC, gelling agent, Franz diffusion, Weibull kinetics

INTRODUCTION

Nowadays, the prevalence of pain disorders is significantly increasing, pushing patients into the consumption of pain-relieving medications. In today's practice, NSAIDs are still extensively persuasive and consumed drugs in their efficient pain and anti-inflammatory effect (Day and Graham, 2013). They are indicated in rheumatic and musculoskeletal disorders (Magni *et al.,* 2021). Their long-term usage poses serious gastrointestinal complications like ulceration, irritation, and bleeding. It is therefore imperative to switch to an approach that prevents toxicity in the gastric environment. To circumvent this, topical drug delivery has attained considerable attention and popularity owing to its numerous favorable aspects such as the ease of administration, local effects, avoidance of hepatic metabolism, preclusion of gastrointestinal toxicity, and improved patient compliance (Azizi *et al*., 2019, Roberts *et al*., 2021). Different gelling polymers are widely utilized due to some special features such as gelation properties and viscosity. Here, lutrol® F 127 has been the perfect fit since it has good solubilization properties (Russo and Villa, 2019). Carbopol 940 has been extensively used due to its higher viscosity and non-irritating effect on the skin (Jana *et al*., 2014). HPMC and CMC have also proved to be biocompatible with good hydration and gel-forming properties (Noval *et al*., 2020, Rahman *et al*., 2021). All these polymers certify their usage in topically applied formulations and also have global regulatory acceptance. Herein, dexibuprofen (fig. 1) is used as a model representative NSAID. It is the racemic form of ibuprofen (Gliszczyńska and Sánchez-López, 2021). Its mechanism of action is to inhibit the activity of the enzyme cyclooxygenase (COX-2); known to be responsible for the synthesis of prostaglandin. Hence the blockage of prostaglandin synthesis leads to producing the analgesic and anti-inflammatory effect in the body (Burki *et al*., 2020). Dexibuprofen is indicated as an anti-arthritic and osteoarthritic agent (Tran and Park, 2021). Moreover, the parenteral mode is not recommended for chronic diseases. Therefore, considering the topical application of this drug would prove to be perfect for pain management. The focus of the current study is the formulation development of an analgesic and ant-inflammatory gel of dexibuprofen to

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improve patient compliance and avoids adverse effects of the oral formulation. The influence of different gelling polymers was explored. The developed trials were tested for physicochemical characterization. In vitro kinetics was studied by applying various models to the drug release data. The best formulation with acceptable organoleptic and physicochemical properties was exposed to accelerated stability conditions. The development of a gel dosage form would be a prospective approach instead of oral tablets as no commercial formulation of dexibuprofen gel is currently available in the Pakistani market yet.

MATERIALS AND METHODS

Chemicals and reagents

Dexibuprofen has been received from S.J.&G Pharma Pvt. Ltd. Formulation additives: hydroxyl propyl methyl cellulose(HPMC), carboxy methyl cellulose (CMC), carbopol 940, lutrol® F 127, methylparaben, ethylene diamine tetra acetic acid (EDTA), ethanol (absolute), propylene glycol were of analytical grade and purchased from the market. Acetonitrile (HPLC grade) was utilized for content analysis. All chemicals were supplied by Sigma-Aldrich and BDH laboratory.

Instrumentation

Electronic balance (Shimadzu librorEB-430-S), hot plate magnetic stirrer (Ms-300/400), vortex mixer (Laboratory FSA Supplies), viscometer (Brookfield DV II Pro viscometer), sonicator (Elma, Germany), pH meter (Jenway 370, England), Franz diffusion apparatus (EMFDC 06, Orchid Scientific, India), Spectrophotometer (Shimadzu UV-1800), HPLC (Shimadzu UV-1800), and stability chamber (Nuaire).

Software

DD-Solver® menu-driven add-in for Microsoft Excel to compute *in vitro* drug release kinetics. Statistical stability CRAN package R-Gui (Version 0.4.9) was used for shelf-life computations based on drugs' assay findings.

Formulation design of dexibuprofen (5%) gel trial formulations

Four dexibuprofen gel formulation batches (DEX-I, DEX-II, DEX-III, and DEX-IV) were prepared using HPMC, CMC, carbopol 940 and lutrol® F 127 polymers. In each batch three different concentrations of polymers were added, keeping the other formulation ingredients constant. HPMC, CMC, and carbopol were tested at 1%, 1.5% and 2% concentration while lutrol® F 127 was added in 8%, 10% and 12% proportions constituting the final formulation. Overall, 12 trial formulations were developed in such a way that three different levels of the same polymer were utilized in each batch. HPMC, CMC, carbopol and Lutrol® F 127 were presented as DEX-I (TD1, TD2, TD3), DEX-II (TD4, TD5, TD6), DEX-III (TD7, TD8, TD9) and DEX-IV (TD10, TD11, TD12). The formulation composition of various trial batches of dexibuprofen gel trials is given in table 1.

Preparation of dexibuprofen (5%) gel trial formulations

Accurately weighed quantities of methyl paraben and EDTA were dissolved in a small amount of hot distilled water (DW) on a magnetic stirrer. Then gelling polymer (CMC, HPMC, carbopol 940, lutrol F 127) was added and kept at rest for 24 hrs. (beaker A). Separately propylene glycol and ethanol were mixed and then dexibuprofen was incorporated into a magnetic stirrer (beaker B). The contents of beaker B were then added to beaker A. Finally, the weight of the gel was adjusted with a quantity sufficient purified water with continuous stirring. The prepared dexibuprofen gel (5%) was stored in a glass jar and kept at room temperature for testing.

Characterization of gel trial formulations

Organoleptic Observations

All the developed formulations of dexibuprofen gel (TD1 to TD12) were characterized for their quality attributes including color, texture, odor, phase separation, and homogeneity at room temperature.

pH determination

Bench top digital pH meter was calibrated with standard buffer solutions of pH 4, 7 and 10 before the determination of the pH of trial gel formulations. Dispersions of trials were prepared by adding 1gm of gel content in 100mL of deionized water (Modasiya, Prajapati *et al*., 2015). The pH of the trials was noted in triplicate.

Spreadability test

Spreadability was performed by the wooden glass slide method. A 0.5 gm of gel sample was placed on a circle of 2 cm diameter covered with the second glass plate. 0.5 Kg of weight was applied on the glass plate for 5 min. Finally, the diameter of the gels after spreading was calculated (Shinde *et al*., 2012).

Rheological assessment

The Brookfield viscometer was used to determine the consistency of the developed gel formulations at room temperature. The gel was placed in a beaker with the spindle immersed in the vertical direction and rotated at 100 rpm (Patel *et al*., 2012). Three consecutive readings were taken and results were expressed in the centipoises (cp).

Pharmaceutical assay

Drug assay of gel formulations were performed using high pressure liquid chromatography (HPLC) technique. The chromatographic procedure was followed using a column made of stainless steel (25 cm x 4.6 mm). The mobile phase was prepared by mixing ortho phosphoric acid (3 volumes), water (247 volumes) and methanol (750 volumes), the peak was observed at 264 nm (Pharmacopoeia, 2017).

Table 1: Formulation Composition (% w/w) of 5%Dexibuprofen (100g) trial gel Formulations (TD1-TD12)

Codes	HPMC (K4M)	CMC	Carbopol (940)	Lutrol F 127	Methyl Paraben	Absolute Ethanol	Propylene glycol	EDTA	Drug	Distil Water (QS)
DEX-I										
TD1	1	-	-	-	0.15	10	12	0.1	5	QS
TD2	1.5	-	-	-	0.15	10	12		5	
TD3	2	-	-	-	0.15	10	12		5	
DEX-II										
TD4	-	1	-	-	0.15	10	12	0.1	5	QS
TD5	-	1.5	-	-	0.15	10	12		5	
TD6	-	2	-	-	0.15	10	12		5	
DEX-III										
TD7	-	-	1	-	0.15	10	12	0.1	5	QS
TD8	-	-	1.5	-	0.15	10	12		5	
TD9	-	-	2	-	0.15	10	12		5	
DEX-IV										
TD10	-	-	-	8	0.15	10	12	0.1	5	QS
TD11	-	-	-	10	0.15	10	12		5	
TD12	-	-	-	12	0.15	10	12		5	

Table 2: Organoleptic evaluation of various trial batches of dexibuprofen gel (5%)

Batch Code	Formulation Trial	Appearance	Consistency	Homogeneity	Texture	Remarks
DEX-I	TD1	Opaque, Low Viscosity gel with intense precipitation	++	-	Gritty	Unsatisfactory
	TD2	Low to medium viscosity Gel with moderate precipitation	+ +	-	Gritty	Unsatisfactory
	TD3	Viscous Gel with few Precipitation	+ ++	++	Gritty	Unsatisfactory
DEX-II	TD4	Very low viscosity gel with no precipitation	-	+++	Smooth	Unsatisfactory
	TD5	Low viscosity gel with no precipitation	+ +	+ +	Smooth	Satisfactory
	TD6	Clear transparent viscous gel with no precipitation	+ + +	+ + +	Smooth	Satisfactory
DEX-III	TD7	Clear transparent viscous gel with slight precipitation	+++	-	Gritty	Unsatisfactory
	TD8	Moderately viscous gel moderate precipitation	++	-	Gritty	Unsatisfactory
	TD9	Viscous Gel with few precipitation	++	-	Gritty	Unsatisfactory
DEX-IV	TD10	Clear, adhesive, low viscosity gel with no precipitation	++	+++	Smooth	Satisfactory
	TD11	Clear, adhesive moderate viscosity gel with no precipitation	++	+++	Smooth	Satisfactory
	TD12	Clear, adhesive, high viscosity transparent gel with no precipitation	+++	+++	Smooth	Satisfactory

+++Good ++ Fair - Poor

Table 3: Physical evaluation of trial dexibuprofen (5%) gel formulations

Batch Code	Formulation Trial	Viscosity (mPa.s)	pH	Spreadability g.cm/sec (n=3)	Assay (%) (n=3)
DEX-I	TD1	590	5.31	7.95 ± 0.04	82.49± 0.76
	TD2	700	5.10	7.35± 0.52	79.85± 1.26
	TD3	753	5.48	6.87 ± 0.12	79.17± 2.20
DEX-II	TD4	895	5.28	12.13 ± 0.27	89.09± 1.73
	TD5	904	5.28	11.08 ± 0.05	88.17±0.97
	TD6	1571	5.55	11.24 ± 0.07	91.32± 2.42
DEX-III	TD7	968	5.32	6.61 ± 0.41	84.19± 1.67
	TD8	856	5.40	5.70± 0.04	86.59±0.91
	TD9	1320	5.60	5.29± 0.03	80.11± 2.01
DEX-IV	TD10	36200	5.30	6.91 ± 0.08	91.26± 1.03
	TD11	44326	5.58	6.49 ± 0.02	89.86± 0.46

Table 4: Drug Release pattern of selected dexibuprofen (5%) gel trials

Code	Zero Order			First Order Reaction			Higuchi Model			Korsmeyer-Peppas Model				Weibull Model			
	K_0	r^2	AIC	MSC	$k_1(h^{-1})$	r^2	AIC	MSC	$k_H(h^{-1/2})$	r^2	AIC	MSC	K_{KP}	r^2	n	AIC	MSC	α	B	r^2	AIC	MSC
5	1.25	0.900	45.648	1.390	0.030	0.980	32.812	3.220	10.635	0.987	31.556	3.403	8.239	0.989	0.563	32.519	3.265	21.878	0.871	0.988	31.427	3.421
TD6	1.27	0.725	55.239	0.040	0.059	0.958	40.078	2.125	13.541	0.929	45.775	1.314	26.624	0.982	0.311	37.928	2.432	7.533	0.709	0.987	33.638	3.045
TD10	1.25	0.7317	54.773	0.107	0.050	0.959	39.546	2.282	12.609	0.930	45.293	1.461	25.229	0.965	0.313	42.455	1.867	10.355	0.768	0.9776	37.381	2.259
TD11	1.21	0.739	54.065	0.002	0.053	0.934	42.414	1.666	12.840	0.937	44.098	1.426	24.841	0.989	0.315	33.745	2.905	7.008	0.648	0.990	31.157	3.275
TD12	1.28	0.610	57.005	0.290	0.068	0.963	39.771	2.221	12.229	0.892	49.272	0.863	32.198	0.971	0.271	42.107	1.884	7.310	0.741	0.981	36.859	2.637

Table 5: Stability Testing of Selected dexibuprofen (5%) gel trial Formulations

Parameters	Time (30 days)			Time (60 days)			Time (90 days)		
	TD6	TD11	TD12	TD6	TD11	TD12	TD11	TD12
Appearance	Clear, transparent, viscous, no precipitation	Clear, adhesive, moderately viscous, no precipitation	Clear, transparent, adhesive, viscous, no precipitation	Precipitation with phase separation	Clear, adhesive, no precipitation	Clear, adhesive, no precipitation	Clear, adhesive, no precipitation	Clear, adhesive, no precipitation
Color	White	White	White	Creamy white	White	White	White	White
pH	5.55	5.58	5.60	5.82	5.53	5.64	5.54	5.64
Viscosity	1571	44326	5000	Low	Moderate	Moderate to High	Moderate	Moderate to High

Optimization of dexibuprofen gel formulations

Based on the physical characterization, formulations that appeared to be homogenous and intact without phase separation were further exposed to drug release kinetics and accelerated stability studies. Formulations that fulfilled the physical and chemical stability criteria for six months are considered to be optimized dexibuprofen gel trials.

In vitro drug release kinetics

Six-cell digital Franz diffusion apparatus was used to assess the amount of drug release from the developed gel formulations. The apparatus was equipped with thermostat water jacket, Nylon membrane, and donor and receptor compartments. The temperature was maintained at 32±0.5°C along with the rotation of magnetic beads set at 100rpm. 2gm gel sample was placed over the membrane and the process continued till 2hr. The samples were filtered and analyzed (Ali, Muhammad *et al*., 2018).

Model fitting of in-vitro drug release data

To apprehend the kinetics of drug discharge, the outcomes of drug release were fitted to drug kinetic models. The data was entered in the DD solver and fitted to zero order, first order, Higuchi and Korsmeyer-peppas model. The best-fitted model based on values of correlation coefficients was taken as criterion for selecting the appropriate model. The kinetic models applied are presented below in equations 1-4: (Farooqi, Yousuf *et al*., 2020).

Zero order: $\text{Log}[-\text{In}(1-m)]=b\ \log(t-T_i)-\log a$ (1)

First order: $\log Q = \log Q_0 - \frac{kt}{2.303}$ (2)

Higuchi kinetic model: $Q=kt^{1/2}$ (3)

Korsmeyer-peppas model: $\frac{M_t / M_\infty}{t^n}$ (4)

Stability studies

Based on quality parameters, selected dexibuprofen trial gel (5%) formulations were subjected to stability studies for three months at 25°C (room temperature) (Borman and Elder, 2017). The gel samples were examined at 1, 2 & 3 months for the evaluation of physical appearance, color, pH, and viscosity. The contents were determined by the HPLC technique using the same method as used for drug's assay.

RESULTS

In the current investigation, different formulations of dexibuprofen gel (5% w/w) were prepared using common gelling agents. All batches of dexibuprofen gel were assessed for their organoleptic characterization (appearance, consistency, homogeneity, and texture) by visual appearance after the gels have been settled in the container. Among trial gels, TD5, TD_6, TD_{10}, TD_{11} and TD_{12} showed satisfactory organoleptic properties. The

details of each trial along with the batch are provided in table 2. Physico-chemical parameters were also evaluated to select the optimized gel formulation(s). The pH of dexibuprofen gel ranged between 5.10 to 5.60. Formulations possessed optimum viscosity and spreadability (table 3). Drug release pattern was also assessed and it was observed that gel trials followed the Weibull model with regression values greater than 0.999, AIC 31.427-37.381 and MSC 2.259-3.421. *In vitro* release kinetics of various other models is presented in table 4. Table 5 showed the stability results that were assessed at 30, 60, and 90 days. Based on the findings, TD11 & TD12 were found to be optimized dexibuprofen (5%) gel trials.

DISCUSSION

Topical formulations are an advantageous approach due to prolong residence time, high viscosity, occlusiveness, and non-irritating effect on the skin (Cojocaru *et al*., 2015). The present study investigates the influence of different gelling polymers at three different concentrations on the release behavior and stability profile. Total of four batches (DEX-1, DE-II, DEX-III, and DEX-IV) were developed. Each batch contained four trials such as HPMC (K4M), CMC, carbopol 940, and leutrol F127 respectively. The selection of penetration enhancers in topical formulations helps to establish good solubility and permeation characteristics. Propylene glycol is extensively reported to be an effective penetration enhancer (Carrer *et al*., 2020). It solubilizes the drug and also modifies the rate of absorption by forming microcavities leading to increase drug diffusion (Kis *et al*., 2022). This approach is found to be extremely beneficial in case of the poorly soluble drugs due to the structural modifications made by chemical enhancers. In the present work, formulations were developed using propylene glycol as dexibuprofen is a BCS-class II drug having poor solubility. Co-solvents have been also utilized as penetration enhancers. Different structural alcohols are commonly consumed in the domain of solubility improvement. Recently a study was conducted by Tian and co-workers to prepare drug-loaded lyotropic liquid crystalline gel using a combination of two alcohol derivatives including menthol and propylene glycol to modify the permeation of the drug. Results depicted that both chemicals enhanced the drug's penetration inside the skin however; menthol did it to a higher extent rather than propylene glycol (Tian *et al*., 2020) Hashmat and the team also endorsed the significant role of propylene glycol in the formulation of controlled-release lornoxicam gel patches (Hashmat *et al*., 2020).

The physicochemical attributes of different developed gel trials were determined using various quality control tests. The pH was recorded in the range of 5.1-5.6. This pH is found suitable for topical application and would not produce skin irritation. The viscosity of the gel is another parameter that greatly influences the consistency. As seen from the table 3 all HPMC polymer-based trials (batch DEX-1) produced low viscosity (609cp to 755 cp) and also showed precipitates formation therefore disqualified from the study. The formulation containing CMC polymer (DEX-II) maintained the smooth texture with no sign of precipitation in TD4, TD5 and TD6. However, the viscosity was not appropriate (liquefied consistency) and therefore was also rejected. The lower viscosity was attributed due to the decreased concentration of polymer in the gels. Likewise, incorporation of the carbopol 940 imparted good gelling consistency but also resulted in precipitation (TD7, TD8 and TD9). Finally, leutrol F 127 delivered successful outcomes. The trials FD10, FD11 and FD12 were elegant in appearance with translucent appearance smooth texture and free from grittiness. The viscosity of FD10, FD11 and FD12 ranged from 36000 to 54000 cp. The developed trials were viscous as they contain a higher concentration of polymer network in the gel. The spread ability was also performed as it is one of the features of topical formulations due to its uniform application over the skin. Here, the spreadability was observed between 5.2±0.03 to 12.1±0.27 $cm^{2.}$ Hence, the prepared trials delivered a higher value of spreadability in lesser time. Further, the trials with satisfactory formulation attributes were subjected to an in-vitro diffusion study. For this, the Franz diffusion cell apparatus was utilized to obtain the release data of TD5, TD6, TD10, TD11 and TD12. Presently, nylon membranes were preferred for the diffusion studies of dexibuprofen (Ng, Rouse *et al*., 2012). Since FDA enforces the use of synthetic porous membranes for the assessment of topical formulation as they are economical, exhibit resemblance with the skin tissue and do not interfere with the rate-limiting mechanism (Ali *et al*., 2018). It is clear that the percentage of dexibuprofen gel is inversely proportional to the percent amount of polymers added into the trial. Like in the case of leutrol F 127, the drug release was found to be slower as the concentration of this macromolecule was increased. This might be related to the complex gel formation leading to drug entrapment and consequently slower release. The results obtained from drug release were fitted to various drug kinetic models. The values of Akaike Information Criterion (AIC), and the Model Selection Criterion (MSC) were determined. It has been documented that higher AIC and lower MSC were also computed to decide the actual kinetic behavior. These parameters are documented in literature by scientists to predict the appropriate dissolution model for the experimental trials where the regression values were much similar to other models (Rabia *et al*., 2018).Overall, the Weibull model was found to be good fit for drug release (r^2>0.999, AIC, MIC). Alpha and beta are the terms used to describe the shape of the release curve. Here the values of (β) for TD5, TD6, TD11, and TD12 were observed as less than 1. The

stability testing of TD5, TD6, TD10, TD11 and TD12 was carried out over six months at accelerated conditions to ensure the product is safe to be applied topically. During the stability period, physical appearance including texture, clarity, color, pH, and viscosity was examined. A detail of the stability report is provided in the result section. Tested formulations were remained stable for one month. However, TD5 and TD10 showed grittiness and did not maintain the actual gelling consistency. While, in the third month of stability testing, trial TD6 was affected physically by phase separation and precipitate formation. In fact, only trials TD11 and TD12 were observed stable and optimized and maintain their appearance, texture, color and pH.

CONCLUSION

The findings of the study showed that dexibuprofen could be used successfully to develop a gel formulation. The lutrol F127-based formulation possessed satisfactory viscosity, spreadability, and pH. The lutrol-containing trials followed Weibull kinetics with regression values greater than (0.977). Based on the experimental findings, it was concluded that TD11 and TD12 were optimized and stable dexibuprofen gel preparations and the proposed study appears to be a favorable to administer dexibuprofen topically.

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