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Formulation and Evaluation of Ibuprofen Gel using a Natural Polymer

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ABSTRACT

Prolonged oral use of ibuprofen for chronic conditions such as arthritis may cause peptic ulcer disease. Topical gel formulations have been developed to overcome this shortcoming. An immediate release formulation of ibuprofen would find application as a transdermal patch for management of chronic inflammatory conditions. In our study, a topical ibuprofen gel was found to have a better release profile for the active pharmaceutical ingredient than the marketed brand.

Key words: Ibuprofen, gel, immediate release, peptic ulcer disease

INTRODUCTION

Non-steroidal anti-inflammatory agents (NSAIDs) are used extensively in the management of inflammatory conditions. Ibuprofen is one of the most commonly used NSAIDs in the treatment of acute and chronic arthritis. The major drawback of NSAID use is risk of gastrointestinal adverse effects such as peptic ulcer disease particularly when used for chronic conditions such as arthritis [1-3]. There is great interest to develop non-oral dosage forms of ibuprofen to minimize its gastric side effects while at the same time delivering consistent drug levels at the application site for prolonged periods. In one study, the efficacy of a topical formulation of ibuprofen 5% gel was shown to have similar efficacy to ibuprofen tablets in the treatment of patients with acute soft tissue injuries whilst avoiding the gastric adverse effects associated with non-selective cyclo-oxygenase inhibitors administered orally [4]. A prolonged release ibuprofen formulation with increased permeability would find application as a transdermal patch for management of chronic inflammatory conditions by relatively providing consistent drug levels for a prolonged period at the site of application.

Ibuprofen, a BCS class II drug, shows poor water solubility and high permeability across the intestinal membrane. Apart from its low intrinsic solubility in aqueous media, it is also known to possess low intrinsic permeability through the skin [5]. Therefore, to dissolve ibuprofen, an organic solvent such as propylene glycol which also acts as a permeation enhancer in most topical formulations is used. Another alternative is to employ guar gum. Guar gum is a galacto-mannose polymer extracted from the guar bean. It is a non-ionic free-flowing, pale, off-white colored powder that forms hydrocolloids. In the pharmaceutical industry guar gum is used as a binder and disintegrant in tablets. A significant advantage of guar gum over propylene glycol is that it has a very large water thickening capacity that is 8 times that of corn starch. Therefore, only a very small quantity is needed to produce sufficient increase in viscosity [6,7].

In vitro release testing plays an important role in drug formulation development and quality control. It can be used not only as a primary tool to monitor the consistency and stability of drug products but also as a relatively rapid and inexpensive technique to predict *in vivo* absorption of a drug formulation [8-10].

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This research was aimed at developing a prolonged release ibuprofen gel using a natural gum and comparing its release profile to that of the marketed gel in an attempt to find a superior alternative.

EXPERIMENTAL

Materials

Ibuprofen powder and guar gum were kind gifts from Regal Pharmaceuticals Ltd (Nairobi, Kenya) while propylene glycol BP and glycerol GPR 98 % v/v were from Sigma-Aldrich Chemie GmbH (Steinheim, Germany). A hot water bath (Baird and Tatlock Ltd, London, UK), a top loading balance (Sartorius AG, Goettingen, Germany), a thermometer (Brannan & Sons Ltd, Cumbria, England), an analytical balance (Shimadzu AUW ZZO D, Shimadzu Corporation, Tokyo, Japan) and a shaking water bath (GFL 1083, Gesellschaft fur Larbortechnik GmbH, Burgwedel, Germany) were employed in the study. Dissolution testing was carried out on an ERWEKA DT 700 dissolution tester (Erweka GmbH, Heusenstamm, Germany). UV-Vis absorbances were read from a T90+ UV/VIS spectrometer (Shimadzu Corporation, Tokyo, Japan). Gel pH was determined on a pH meter (WTW Microprocessor 537, WTW GmbH, Weilheim, Germany).

Preparation of gels

About 3 g ibuprofen was added to 7 ml of propylene glycol and the mixture warmed to 65 °C to form a solution. Gels containing different amounts of guar gum were prepared by warming the gum to 65 °C and mixing it with 15 ml of propylene glycol while stirring thoroughly for 10 min. The ibuprofen solution was mixed with the gel and distilled water added to make up the final weight with vigorous stirring. The ibuprofen containing gel was continuously stirred using a magnetic stirrer for about 20 min until no bubbles were noticed.

Three different ibuprofen gels were prepared by varying the guar gum composition (Table 1).The gels were stored in HDPE plastic containers until the time for analysis.

Table 1: Composition of formulated ibuprofen transdermal gel samples

Formulation	Ibuprofen (g)	PG (g)	Guar gum (g)
F1	3	7	2.5
F2	3	7	5
F3	3	7	10

PG = Propylene glycol

Characterization studies

Homogeneity: The gel was visually inspected after 2 days for its appearance and presence of aggregates.

Texture: The texture was determined by rubbing a bit of the gel on undamaged skin and observing for absence of grittiness.

Surface pH: A pH meter was immersed into a small amount of the gel to determine surface pH of the gel. This was repeated for a marketed ibuprofen gel (Ibumex®).

Drug content: An amount of the formulated gel equivalent to 5 mg ibuprofen was weighed and immersed in a 100 ml volumetric flask containing 80 ml of phosphate buffer (pH 7.4). The flask was stoppered and placed in a mechanical shaking water bath set at 37 °C for 2 h to allow for complete dissolution of the drug and made up to volume with phosphate buffer. A 20 ml aliquot of this solution was withdrawn and placed in a 100 ml volumetric flask and the volume made up using distilled water. The UV absorbance of the solution was read at 222 nm using phosphate buffer (pH 7.4) as the blank.

The ibuprofen content, in µg/ml, was determined from the absorbance value obtained and read against a standard calibration curve. This content was then calculated as a percentage of the expected concentration of ibuprofen.

In vitro release studies

The *in vitro* release of ibuprofen from the prepared formulation and a marketed formulation through cellulose acetate paper was studied using a modified release testing apparatus II. The release medium used was

phosphate buffer pH 7.4. Cellulose acetate paper was soaked for 2 h in phosphate buffer. One gram of the formulated gel (equivalent to 262 mg ibuprofen) and 1 g of the marketed gel (equivalent to 5 g ibuprofen) were weighed onto separate microscopic glass slides. Cellulose acetate paper was then used to completely cover the centre surface of the glass side with gel and sellotape used to completely seal the paper edges. The glass slides were then suspended in 900 ml phosphate buffer solution maintained at 37 ± 0.5 °C. The paddles were rotated at 50 rpm and aliquots of 20 ml withdrawn at 15 min, 30 min, 45 min, 1 h, and thereafter hourly up to the 5^{th} hour. Aliquots were replaced by equal volumes of the phosphate buffer solution. The absorbance of the aliquots was measured at 222 nm. The release profile of 3 samples of the gel was compared to that of 3 samples of the marketed ibuprofen gel. The cumulative percentage drug release was calculated based on the concentrations obtained for the various gels over time as a function of the loading doses (equivalent weight of ibuprofen in 1 g samples of the gel). The concentrations were calculated based on the absorbance obtained and the standard calibration curve. The release profile was explored for the various release models using DDSolver 1.0 Version 2010 (ZhangYong China Pharmaceutical University, China) [11].

RESULTS AND DISCUSSION

The formulated and the marketed gels showed good homogeneity with absence of lumps. The pH range for the formulated gels F1, F2 and F3 was 6.25 - 6.40. This was lower than the pH of the marketed gel (8.17). However, the low pH was still found to be satisfactory as both ibuprofen and guar gum are stable at this pH. In addition, the pH of the formulated gels was closer to skin pH (5.5) thus reducing the possibility of skin irritation.

The average ibuprofen content in the formulated gels was found to be 83.2 % (RSD 2 %) which was satisfactory for this experiment. A greater uniformity in drug content approaching 99 % could probably be obtained if stirring during gel formulation is done using a homogenizer which was unavailable.

A study of the release profile over 5 h revealed that all three formulated gels had a higher percentage of ibuprofen release than the marketed gel as shown in figure 1. Higher cumulative release percentage than the marketed gel implies that therapeutic levels of ibuprofen would be reached faster while maintaining a prolonged release profile. Due to the large water thickening capacity of guar gum, small concentrations are required to initiate gelling and thus economically, this presents an advantage in terms of lower cost of production.

Various model-dependent kinetic modeling approaches were adopted for comparing release profiles of the two gel formulations [12-16]. The models included Korsmeyer-Peppas [17, 18], Higuchi [19] and Weibull [20]. In order to determine the best fit model for the evaluation of ibuprofen release from the hydrophilic gel manufactured in these studies, the r^2 was adopted as the selection criterion. Models with the highest r^2 value were considered the best fit for the data evaluated. A value for $r^2 > 0.99$ was considered acceptable for the purposes of comparison of modeling release profiles generated in these studies. The best fit model parameters obtained following fitting of experimental data obtained from the formulated gel are listed in table 2. The Korsmeyer-Peppas model, therefore, best described the release of ibuprofen from the formulated gels.

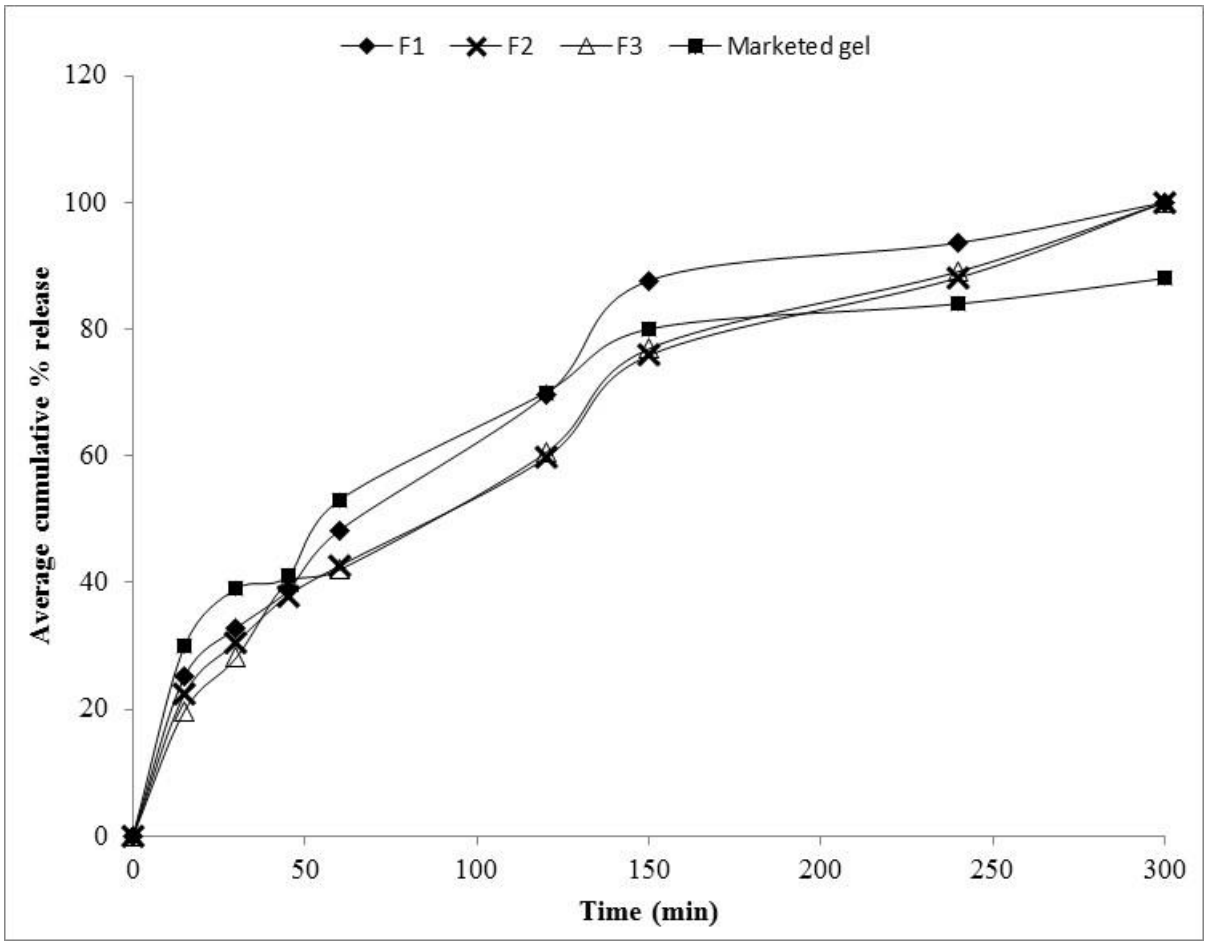

Figure 1: Comparison of release profiles of the formulated gels and the marketed gel

Table 2: Model best-fit parameters for formulated samples of ibuprofen gels

Model	r^2			
	F1	F2	F3	Mean
Korsmeyer-Peppas	0.9948	0.9951	0.9952	0.9950
Huguchi	0.9865	0.9867	0.9866	0.9866
Weibull	0.9858	0.9876	0.9872	0.9867

CONCLUSION

This study successfully demonstrated the formulation of ibuprofen as a prolonged release gel for dermatological application using the natural guar gum. The formulated gels had satisfactory homogeneity and gel texture. The superior release profiles of the formulated gels over the marketed gel make these gels a viable alternative in the management of dermatological (local) and systemic (following percutaneous absorption) disorders characterized by inflammation.

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