Original Article

Bioadhesive Gel and Hydrogel Systems for Buccal Delivery of Ketoprofen: Preparation and *In vitro* Evaluation Studies

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ABSTRACT

Introduction: The studies are focused on buccal system due to advantages such as avoidance of the hepatic first-pass metabolism and better patient medication compliance. Ketoprofen (KP) which is a non-steroidal antiinflammatory, analgesic and antipyretic agent that used as an active substance.
Method: Buccal bioadhesive gels (BG) and bioadhesive hydrogels (BHG) with KP were prepared with Carbopol (CP) 940 and CP 934 as polymers. BG were characterized by determination of rheological properties, mechanical stress and mucoadhesive properties. And also BHG were tested for tensile strength and mucoadhesive properties. The release studies through dialysis bags were performed for all formulations.
Results: BHG for buccal application were formulated by photopolymerization technique for the first time in this study. According to comparing obtained results, it can be suggested that BHG can be offered as promising dosage form for the buccal application.

Keywords: Bioadhesive system, Carbopol, Gel, Hydrogel, Ketoprofen, Photopolymerization technique.

INTRODUCTION

The buccal mucosa is an important route for the treatment of local and systemic application of drugs that have advantages such as overcoming the drawbacks of conventional administration routes. The buccal mucosa is permeable and robust. In comparison with other mucosal tissues, it is more tolerant to potential allergens and has a reduced tendency of irritation or damage. The direct entry of the drug into the

systemic circulation obviates the first pass hepatic effect. And also, active substance can be easily administered and if necessary, removed from application site. Buccal mucosa has been investigated as a potential application site for delivery of drugs in various chronic systemic therapies to achieve local and systemic effect.[1,2]

Gel systems are classical formulations that are using for topical administration of many drugs. They offer various advantageous properties such as easy application, spreadibility and biocompatibility, also showing a number of different remarkable physicochemical properties that make them remerkably systems for different applications in drug delivery systems.[3]

Advanced technologies in polymer chemistry turn the challenges into opportunities of drug release systems. Hydrogels (HG) are a special class of three-dimensional cross-linked polymers synthesized from hydrophilic monomers and/or pre-polymers with the ability to swell or shrink as a response of medium. HG can be tailored and also can be prepared with biocompatible monomers.[4,5] As a result of being tailored, the release of drug can be controlled by controlling amount of monomers correspond to drug release.

They act as drug vehicles by trapping drug molecules within the pores inside of the matrix. As a result of the alteration of the medium, they absorb water and swell. The gaps between crosslinks increase and the drug release occurs. Because of these properties, hydrogels find extensively application for a wide range of biomedical applications such as controlled drug delivery, tissue engineering, regenerative medicine and diagnostic biomedical biosensors.[6,7]

On the other hand, photocurable systems exhibit very rapid rates of polymerization and this advantage may cause to be preferred over the other techniques such as wet chemical crosslinking. Photopolimerization provides less side products, no volatile solvents and homogenous network formation and also does not require heat for polimerization.[8,9]

Various hydrophobic and hydrophilic polymers are used to prepare HG. By the way, in biomedical applications especially hydrophilic and/or pre-polymers are used to produce HG. Polyethylene glycol diacrylate (PEGDA), ethyleneglycol dimethacrylate (EGDMA), poly (hydroxyethyl methacrylate) (p(HEMA)), polyvinyl alcohol (PVA), poly(lactide-coglycolide) (PLG), and natural polymers such as gelatine, chitosan and alginate are some of the examples for hydrophilic monomers and/or pre-polymers.[7] PEGDA and EGDMA are attractive for the synthesis of HG and they are already approved polymers for use in drug release, are considered non-toxic and non-irritant and are commerciallly available.[10-12] PEGDA was chosen to prepare BHG formulations due to non-toxic and water solubility properties of polymer.[13-15]

CP was also added to BG and BHG formulations. CP is a polyacrylic acid polymer and with the increase of pH over than 5.5 it shows a gel transition in aqueous solution and is widely used in mucosal formulations. Moreover, CP exhibits excellent mucoadhesive properties when compared with other bioadhesive polymers. It is a non-toxic, non-irritant and biocompatible polymer.[16,17]

KP, (2-(3-benzophenyl)-propionic acid) is a propionic acid derivative which belongs to the class of non-steroidal anti-inflammatory drugs (NSAIDs), and commonly used for the treatment of ankylosing spondylitis, non-rheumatoid diseases or inflammation and fevers in clinical medicine. KP is also commonly used for the treatment of muscular and

rheumatic pain, sprains, strains, backache, and neuralgia and for the management of the signs and symptoms of rheumatoid arthritis and osteoarthritis, postoperative pain, alleviate pain.[18-20] KP is orally well absorbed and has a short half-life time of 2 hours and it reaches high plasma levels in 0.5-2 hours.[14,19] Due to the fast elimination property of KP from the body, it must be taken up to four times in a day for reducing pain. But revealing high doses may cause adverse effects on stomach, gastrointestinal tract and kidney such as, ulceration, bleeding, irritation and damage of gastric mucosa.[14,19,21-23] In order to prevent this drawback, delayed release KP formulations and enteric coated dosage forms have been improved.[14,19] KP topical patches are being heavily used for treatment of musculoskeletal pain. The formulation of the patches can be controlled and this property provides controlled drug release.[14,21]

The goal of this work is to investigate;

- Preparation of BG and BHG formulation,
- Characterization of formulations for rheological behavior, mechanical properties and *In vitro* release profile.

MATERIALS AND METHODS

Materials

Ketoprofen was a kind gift from Eczacıbası İlaç San. ve Tic. A.Ş. (Turkey). Carbopol® 940 and Carbopol® 934 were provided from Lubrizol Advanced Materials (Cleveland, Ohio). All other solvents and reagents were of analytical grade.

Preparation of bioadhesive gels

CP 940 and CP 934 were selected to prepare BG formulations. CP 940 (G1) or CP 934 (G2) was added into the distilled water while gently stirred at 600 rpm till the gel swelled. Triethanolamine was added with continued stirring to form a transparent gel until the gel had pH 7. 2% (w/w) of KP was added on to the gel while gel mixing by a mechanical stirrer at 600 rpm. The bubbles were removed by centrifugation at 3000 rpm for 15 min. The gel formulations were kept in the refrigerator till characterization studies.[24-26] The composition of BG was given in Table 1.

Preparation of bioadhesive hydrogel formulations

Photopolymerization technique was used to prepare BHG formulations. All polymerization processes were performed at room temperature (climate-controlled). CP 940 (H1) and CP 934 (H2) were used to prepare BHG formulation included or not included KP. Formulations were prepared at three different ratios of CP polymers. Irgacure 184 (Irg 184) was used as photoinitiator. The composition of the formulations was given in the Table 2. The homogenous mixture of all the components was transferred to a Teflon® mold (R=4 mm). Then, the formulations in the mold were irradiated for five minutes with a high pressure UV lamp (OSRAM 300 W, λ_{max}=365 nm). The UV-cured BHG were removed from the mold and held at +4°C.[4]

Characterization of formulations

Rheological studies

The rheological analysis of the formulations was done at 25±0.1°C using Haake Mars Rheometer, in flow modewith parallel steel plate (diameter 40 mm). For continuous shear analysis, flow curves for each formulation were measured over shear rates ranging from 10-2000 s^{-1} with a gap of 0.3 mm (n=5).[16,27]

Oscillatory analysis of each formulation under examination was performed after determination of its linear viscoelastic region at 25.0±0.1°C. Frequency sweep analysis was performed over 0.1-10.0 Hz frequency. The standard

gap size was 0.3 mm for each sample. Storage modulus (G′), loss modulus (G″), the dynamic viscosity (ŋ′) and the loss tangent (tan δ) were established (n=5).[28,29]

Mechanical properties of bioadhesive formulations

Mechanical examination of the BG and BHG were evaluated using Software-controlled penetrometer (TA-TX Plus, Stable Micro System, UK) with 5 kg load cell at 25ºC.

For BG formulations, probe was twice compressed into each formulation to a 15 mm depth and at 2 mm/s rate, allowing 15 s delay period between the compressions. Mechanical parameters as hardness, compressibility, adhesiveness, cohesiveness and elasticity were determined from the resultant force-time curve (n=5).[30]

For evaluation of formulations, BHG samples with standart dimension (50x10 mm) and without air bubbles or physical imperfections were held between two clamps at a distance of 3 cm. A cardboard was attached on the surface of the clamp withtape to prevent hydrogel from being cut by the clamp. During measurement, the strips were pulled by the top clamp at 2.0 mm/s rate of to a distance of 5 cm before returning to the starting point. The force and elongation parameters were determined when the BHG broke. Results from BHG samples, which broke were not included in calculations (n=5).[31,32] Equation [1] was used to calculate the parameters:

Tensile strenght ($N.mm^{-2}$) = Force at break (N) / Sectional area of the sample (mm^2) …….... Equation [1]

Evaluation of the mucoadhesive properties

Mucoadhesion measurements were performed using Software-controlled penetrometer (TA-XT Plus, Stable Micro System, UK) equipped at 37ºC in texture profile analysis (TPA) mode. Mucin disc was attached to the lower end of the probe of the instrument with cyanoacrylate glue. The probe holding the musin disc was lowered on to the surface of the gel with a constant speed of 0.1 $mm.s^{-1}$ and a contact force of 0.5 N were applied. After keeping in contact formulation and mucin disk for 2 min, the probe was then moved vertically upward at a constant speed of 0.1 $mm.s^{-1}$. Maximum detachment force (F) was obtained from the force-distance graph. The area under the curve was calculated from force-distance plot as the mucoadhesion (n=5).

In vitro release study

In vitro release study of bioadhesive gel formulations

The diffusion technique wtih dialysis bag was used to study the *In vitro* release of KP. 1 g formulations were placed in the dialysis bag (cellulose membrane, molecular weight cut off 12.000-14.000 D). The dialysis bags were hermetically sealed and immersed into 80 ml of phosphate buffer (pH 6.8) as simulated salivary fluid. The system was kept at 37±0.5°C with magnetic stirring at 400 rpm. Samples were withdrawn from the receptor compartment and replaced by fresh medium. The amount of drug was determined by spectrophotometer at the 260 nm wavelength. The concentration of active substance was determined via standard curve of KP.

In vitro release study of bioadhesive hydrogel formulations

The diffusion technique with dialysis bag was used to study the *In vitro* drug release of KP from BHG as mentioned above for gel formulations. The weight of BHG was measured before release studies. The amount of drug from BHG was determined by spectrophotometer at the 260 nm wavelength. The concentration of active substance was determined via standard curve of KP and the percentage of released drug was calculated.

RESULTS AND DISCUSSIONS

Rhelogical studies

The rheological studies for the semisolid formulations need to be controlled and understood since it is important for predicting their behavior *in vivo* conditions. The flow properties affects the residence time on the application site and can help predict spreading and covering properties over the mucosal tissue.[30] The flow curves of BG were graphically presented in Figure 1. All of the prepared formulations showed non-Newtonian plastic flow. It was expected due to its semisolid properties. Addition of active substance didn't affect flow properties of formulation. Our results showed similarity with the literatures.[16,34]

The rheological properties of BG can be affect the ease of application and retention. Following buccal application, it is accepted that the equilibrium rheological properties of the formulations will dominate the subsequent physico-chemical properties. A gel formulation should exhibit a solid-like mechanical spectrum; that is, G′>G″ throughout the experimentally and there is little frequency dependence of the moduli.[35,36] Figure 2 represents the frequency dependence of the G″ and G′ of BG. All gels were found frequency independent after certain frequency values and exhibited typical gel-type mechanical spectra (G′>G″). G1-1, G2-1 and G2-2 could be described as strong cross-linked gel formulations and not influenced by the frequency of oscillation.

Mechanical and mucoadhesive properties

TPA is used to identify formulations that may be more suitable for clinical application and also buccal performance of formulations. Buccal formulations should have appropriate mechanical properties for the maximum benefit of the patient from the formulations.

The basic parameters for designing of gel formulation are ease of removal from the primary package, ease of application to the desired region and retention at the application site without disintegration. TPA analysis revealed that prepared formulations had more suitable mechanical properties like hardness, elasticity, cohesiveness and adhesiveness. Mucoadhesive properties are also very important for mucosal formulations for prolonged residence time and a decreased leakage with the mucosal secreation.[37] When we compare our results with previous studies, it was seen that the gel formulations used in this study possessed appropriate hardness, compressibility, cohesiveness and elasticity values. The hardness and compressibility values increased significantly due to increase in polymer concentration. This can be explained by concentration-dependent effects on the formulations' viscosity. Adding to the active substance to the formulations effected to the mechanical properties. After examination of the formulations with the active substance, G1-1 coded formulation exhibited with low hardness and compressibility, high cohesiveness and appropriate mucoadhesiveness and elasticity. Table 3 shows the mechanical properties.

The tensile testing gives an indication of the strength and elasticity of the HG, reflected by the parameter, tensile strength. Tensile strength is relavent with mucoadhesion properties also. A soft and weak polymer can be characterized by a low tensile strength; a hard and brittle polymer can be defined by a moderate tensile strength. Soft and tough polymer is characterized by a moderate tensile strength; whereas a hard and tough polymer is characterized by a high tensile strength. An ideal buccal BHG formulation should possess high tensile strength.[31,32] Our experimental data indicated that H1-3 showed highest tensile strength value than other formulations (Table 4).

The contact time of a formulation on the mucosa is of high importance for buccal drug delivery. Mucoadhesive formulations

have been reported to prolong the residence time of the formulation at the application site. Quantification of mucoadhesion is important to ensure that the adhesion offered by formulations with prolonged retention at the site of application.[38] The work of mucoadhesion of formulations increased with the increase in the polymer concentration. In BHG formulations, H1-3 has higher mucoadhesive properties than other formulations. Also, peak detachment force was used to evaluate the mucoadhesive strength of the hydrogels.[39] According to the results of BHG with active substance, H1-3 has highest detachment force than other formulations. Result of mucoadhesion studies was in accordance with the mechanical properties of formulations. Based on these properties H1-3 appeared to offer optimal mucosal performance.

Release studies

The results of release studies from BG were shown in Figures 3 and 4. As it was seen, the release through G1-1 formulation was found faster than G1-2 formulation (one-way ANOVA, post-hoc test Tukey, $p<0.05$). At the end of 4 hours, 99 and 87% of KP was released from G1-1 and G1-2 formulations, respectively. The release amount of KP from G2-1 was also faster than G2-2 formulation. According to results, it was shown that increasing polymer amount in BG decrease release amount of KP from formulations. G1 and G2 gels were prepared with CP 940 and CP 937 that had different viscosity properties, respectively. It was reported, the amount of polymer in the formulation and viscosity could affect release characteristic of active substance.[40-43] The polymer concentrations were chosen such as 1 and 2 percentage to investigate effect of polymer amount on release behaviour of gel systems.[44-47] As it was shown in Figure 3 and 4; a small difference was observed between G1 and G2 formulations.

The release studies of BG systems were performed as mentioned above. The results were seen in Figure 5 and 6. As it was seen, controlled release was achieved with BHG. The release amount of KP from hydrogel systems was found slower than gel systems. The release from polymeric systems prepared with three concentration of CP 934 and CP 940 were found similar (one-way ANOVA, post-hoc test Tukey, $p>0.05$). By the way, there was a slight difference for KP release from CP 934 and CP 940 BHG formulations.

Baloğlu *et al*. prepared solid bioadhesive formulations and it was concluded that different polymers had different release profile. The release amount was decrease while polymer concentration and viscosity increase.[48] And also swelling capacity of polymer was another parameter that designate release amount.[49-50] In our study, the release amount of KP through BG formulations was decrease with increasing polymer concentration. In the case of BHG formulations, the release amount of KP was found nearly same. The all of the BHG formulations prepared with high and same amount of PEGDA. Therefore it was though that effect of polymer on release was decrease.[51,52]

CONCLUSION

This study focused on the development of BHG and BG formulations containing KP for buccal administration. Formulations were characterized in terms of textural, rheological, mucoadhesive and release properties. According to the BG characterization results, G1-1 formulation could be a good candidate for buccal administration with suitable textural properties, high mucoadhesive value, strong gel properties and release behaviors. According to the BHG characterization results, H1-3 formulation could be a good candidate for buccal administration with

suitable mechanical and mucoadhesive properties.

Competing interest

The authors declare that there is no competing interest, and all authors participated actively in the work. All authors read and approved final version of manuscript for publication.

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Table 1. The composition of BG formulations prepared with CP 940 and CP 934

Formulation code	KP (%)	CP 940 (%)	CP 934 (%)
G1-1b	-	1	-
G1-1	2	1	-
G1-2b	-	2	-
G1-2	2	2	-
G2-1b	-	-	1
G2-1	2	-	1
G2-2b	-	-	2
G2-2	2		2

Table 2. The content of BHG formulations prepared with CP 940 and CP 934

Formulation code	KP (g/g)	CP 940 (%)	CP 934 (%)	PEGDA (%)	EGDMA (%)	Irg 184 (%)	H_2O (%)
H1-1b	-	1	-	97	3	3	20
H1-1	0.02	1	-	97	3	3	20
H1-2b	-	2.5	-	97	3	3	20
H1-2	0.02	2.5	-	97	3	3	20
H1-3b	-	5	-	97	3	3	20
H1-3	0.02	5	-	97	3	3	20
H2-1b	-	-	1	97	3	3	20
H2-1	0.02	-	1	97	3	3	20
H2-2b	-	-	2.5	97	3	3	20
H2-2	0.02	-	2.5	97	3	3	20
H2-3b	-	-	5	97	3	3	20
H2-3	0.02	-	5	97	3	3	20

Table 3. Mechanical and mucoadhesive properties of the BG formulations

Formulation Codes	H±SD (g)	C±SD (g.sec)	Ch±SD	E±SD	M±SD (mJ)
G1-1b	0.454±0.029	1.004±0.195	0.933±0.043	0.698±0.076	0.135±0.054
G1-1	0.189±0.029	0.476±0.022	0.980±0.032	0.678±0.025	0.131±0.018
G1-2b	0.593±0.033	1.350±0.118	0.920±0.052	0.832±0.128	0.168±0.011
G1-2	0.415±0.002	0.975±0.073	0.943±0.058	0.869±0.111	0.156±0.044
G2-1b	0.349±0.009	0.913±0.097	0.927±0.028	0.829±0.042	0.099±0.013
G2-1	0.190±0.011	0.258±0.048	0.952±0.107	0.667±0.064	0.091±0.080
G2-2b	0.358±0.015	0.808±0.066	0.934±0.013	0.674±0.081	0.095±0.018
G2-2	0.339±0.002	0.666±0.009	0.862±0.035	0.589±0.023	0.093±0.035

H: Hardness; C: Compressibility; Ch: Cohesiveness; E: Elasticity; M: Work of adhesion.

Table 4. Mechanical and mucoadhesive properties of BHG formulations

Formulation Codes	Tensile strenght (N/mm^{-2})	F±SD (N)	M±SD (mJ)
H1-1b	0.168±0.023	0.034±0.017	0.071±0.015
H1-1	0.310±0.082	0.026±0.000	0.048±0.005
H1-2b	0.302±0.079	0.056±0.007	0.116±0.006
H1-2	0.316±0.090	0.048±0.007	0.115±0.000
H1-3b	0.358±0.061	0.144±0.017	0.171±0.035
H1-3	0.317±0.124	0.089±0.008	0.131±0.005
H2-1b	0.185±0.019	0.022±0.002	0.084±0.027
H2-1	0.238±0.091	0.020±0.001	0.080±0.028
H2-2b	0.235±0.036	0.055±0.012	0.093±0.021
H2-2	0.265±0.121	0.052±0.002	0.092±0.002
H2-3b	0.316±0.091	0.096±0.034	0.128±0.014
H2-3	0.291±0.061	0.090±0.072	0.123±0.021

F: Maximum detachment force; M: Mucoadhesion.

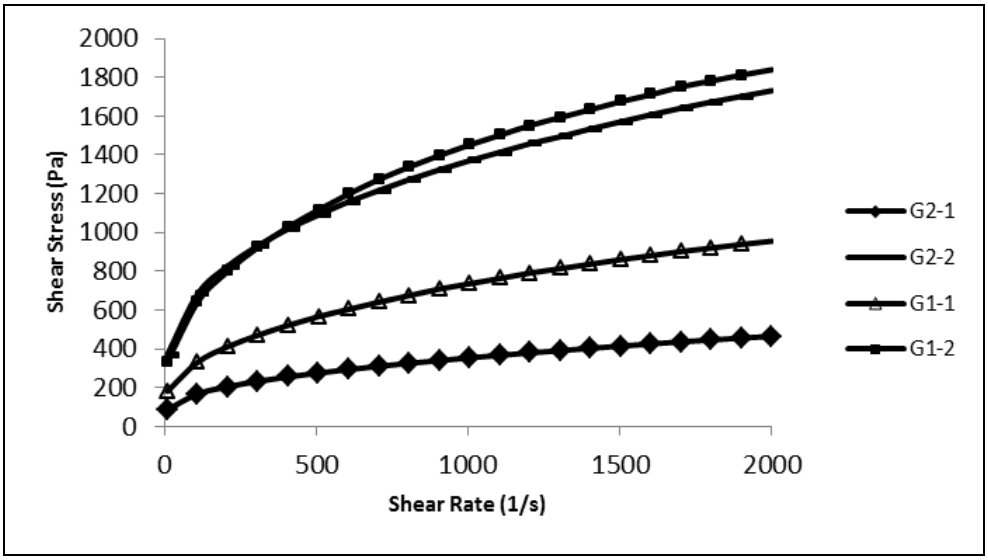

Figure 1. Flow curves of the gel formulations

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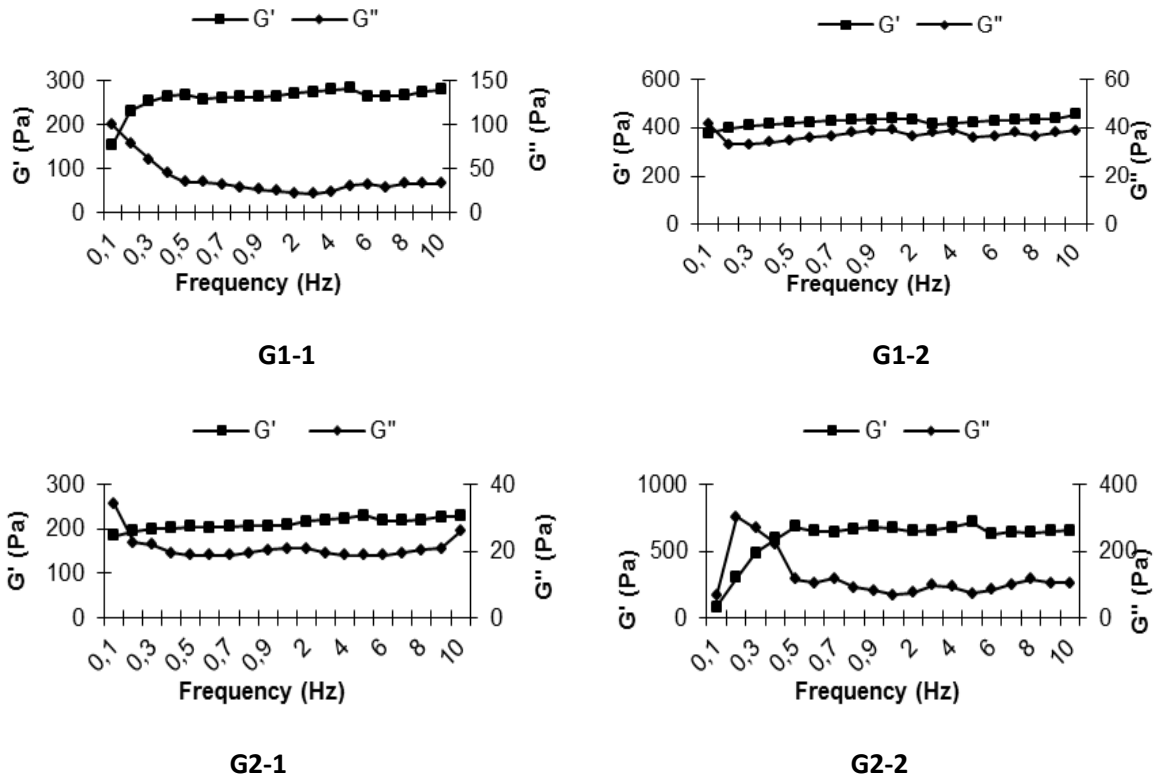

Figure 2. Frequency-dependent changes of viscoelastic properties of the BG formulations

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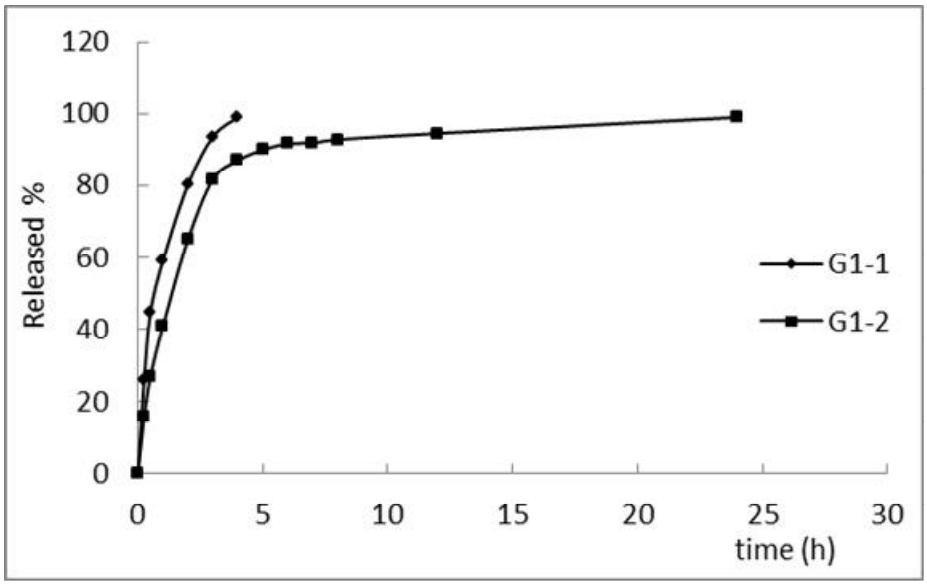

Figure 3. Release profile of KP through G1 formulations

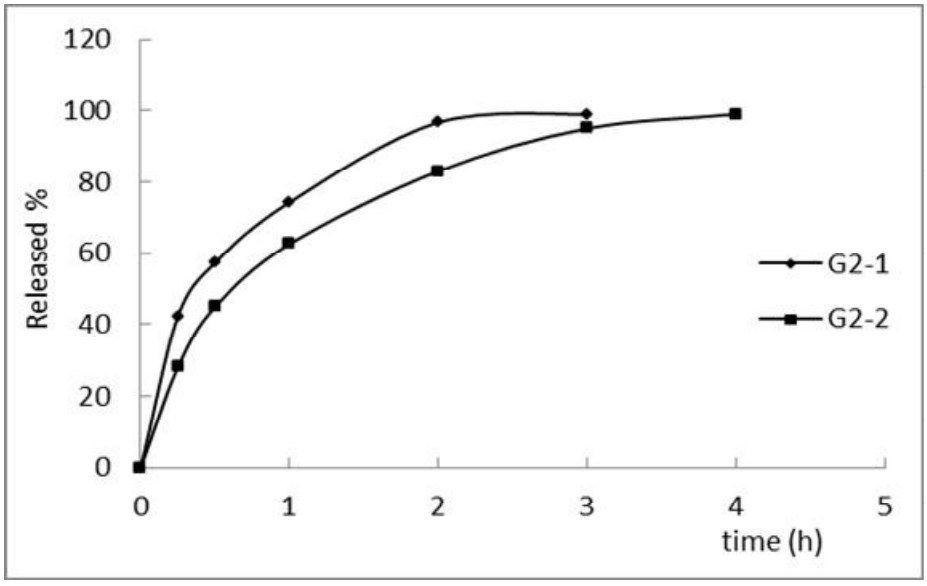

Figure 4. Release profile of KP through G2 formulations

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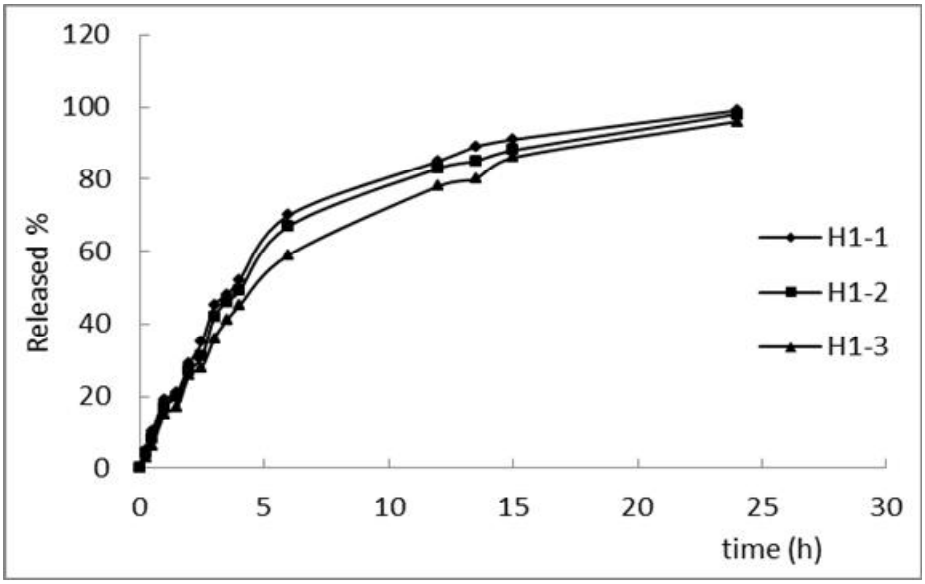

Figure 5. Release profile of KP through H1 formulations

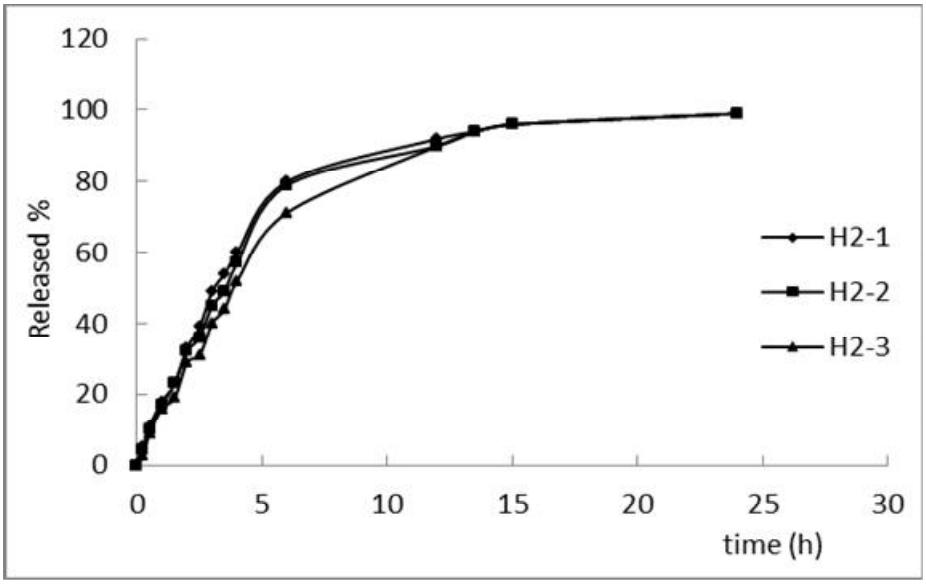

Figure 6. Release profile of KP through H2 formulations