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Research article

Formulation and characterization of amlodipine loaded *in-situ* film forming hydrogen for dermal drug delivery

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ABSTRACT

Present work involves the development of novel *in situ* film-forming hydrogels (FFH) consisting of primarily Carbopol 934P, HPMC E50 LV and PEG 400. Here, propylene glycol was employed as a permeation enhancer for studying its effect in the formation of FFH and drug permeation. Prepared formulations were assessed for various parameters. Prepared FFH was uniform in weight and thickness with acceptable pH, viscosity and spreadability. Prepared FFH was able to form the *in- situ* film on the skin surface within 7min. propylene glycol was found to have a direct relationship with moisture content, moisture uptake and water vapour transmission. Higher drug encapsulation and better permeation were also observed when concentration of propylene glycol was increased. All formulations were non-irritating to the skin and thus acceptable. In conclusion, prepared *in-situ* film-forming hydrogel can be effectively used as a novel dermal drug delivery system.

Keywords: In-situ Film,Dermal Drug Delivery, Amlodipine.

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INTRODUCTION

Amlodipine is a calcium channel blocker that is primarily used as an antianginal drug [1]. Amlodipine is a second- and third-line medication that works by altering the calcium channel in the vascular muscles to lower blood pressure [2]. Its use, however, is not confined to the treatment of cardiovascular disease. Antioxidant, apoptotic, anti-inflammatory [3], and wounds healing [4] have all gained popularity in recent years as another uses of amlodipine. However, because amlodipine absorbs slowly and suffers considerable first-pass metabolism when administered via traditional methods, it must be administered by an alternate route in an appropriate drug delivery system (DDS) [5]. This needs the development of a transdermal drug delivery method in order to improve amlodipine's efficacy, stability, and bioavailability. DDS for the cutaneous administration of amlodipine has been the subject of some research. A transdermal patch is one such DDS that aids in sustained drug administration [6-9], plasma concentration maintenance for up to 72 hours, and elimination of first-pass metabolism [7]. a study in 2009 that identified film as a promising DDS. However, these systems were discovered to have a number of flaws. However, these systems have a number of limitations, including complicated preparation procedures, pain while removing the patch or film, and patient noncompliance, all of which can be solved with the gel-based system [9-10].

In this case, making a film-forming hydrogel can be beneficial because it combines the benefits of a film/patch with a gel [11].

In-situ film-forming hydrogel (FFH) is a semisolid DDS that includes using a solvent evaporation process to convert gel into a protective, flexible, and occlusive film over the body's applied surface [12]. Topical medicines such as gel, cream, and ointments easily wipe off from the surface, but FFH has an advantage over this. FFH stays intact on the site for a long time, allowing for superior stability, controlled drug release, and penetration [13]. Because FFH combines the advantages of gel and film/patch, it can be used to create an in-situ film forming hydrogel loaded with amlodipine, which has not to be reported yet. By avoiding the extensive first pass metabolism seen with oral amlodipine delivery, prepared FFH can improve drug bioavailability. As a result, the present research includes making FFH with carbopol 934 as a gelling agent and HPMC E50 LV as a film former. Propylene glycol was also added as a permeation enhancer to see how it affected drug penetration. The appearance, pH, viscosity, spreadability, and film-forming time of the FFH were all evaluated. The moisture content, drug content, water vapour transmission test, rolling ball tack test, and bio-adhesion test were all performed on the in-situ film. To test its acceptability, an in-vitro drug release and skin irritation study was also done.

MATERIALS AND METHODS

Materials

Amlodipine besylate, Carbopol 934P, HPMC E50 LV, PEG 400 and glycerol were procured from Central drug house (P) Ltd. New Delhi, India. All reagents used were of analytical grade.

Development of In-Situ Film Forming Hydrogel (FFH)

HPMC E50 LV, Carbopol 934, PEG 400, glycerol, and propylene glycol was used in the preparation of in-situ film-forming hydrogel, which was prepared with the help of a mechanical stirrer (Table 1). To obtain the polymer dispersion, the ethanolic HPMC E50 LV (6 percent w/v) solution was slowly added to Carbopol 934 (1.5 percent w/v) solution while continuously stirring. The drug was then added to the polymer dispersion while it was still being stirred, followed by PEG 400 and glycerol. The resulting system is then agitated at 1200rpm for around 30 minutes to obtain the FFH, which is then kept appropriately in an airtight container until needed. Due to the evaporation of solvent from the produced FFH, the in-situ film is obtained after exposure to a surface [14].

Table 1: Formulations to Determine the Effect of Propylene Glycol PG in preparation of FFH

Ingredients	Formulation code					
	FF0	FF1	FF2	FF3	FF4	FF5
Amlodipine besylate (%)	0.2	0.2	0.2	0.2	0.2	0.2
HPMC (E50LV) (%w/v)	6	6	6	6	6	6
Carbopol 934P (%w/v)	1.5	1.5	1.5	1.5	1.5	1.5
PEG 400 (%v/v)	10	10	10	10	10	10
Glycerine (%v/v)	0.4	0.4	0.4	0.4	0.4	0.4
Ethanol (%v/v)	40	40	40	40	40	40
Water (%v/v)	60	60	60	60	60	60
Propylene glycol PG (%v/v)	0	6	7	8	9	10

Characterization of FFH

FFH was initially characterized for appearance, pH using a digital pH meter [15], viscosity using rotating spindles in a Brookfield viscometer [19], spreadability, and film-forming time on a glass slide (2cm^2 area) at 25°C. For spreadability test, 500mg of gel was placed between two horizontal glass plates, which were then loaded with 500g of weight. The diameter was measured after 10 minutes of weighing, and the extent of spreadability was determined by the difference of initial and final area [16].

Characterization of *In-Situ* Film

FFH exposure to surface results in the formation of an *in-situ* film was investigated for moisture content, drug content, water vapour transmission test, rolling ball tack test and bio-adhesion test. Weight uniformity test was conducted by using an analytical balance for measuring the weight of 1g gel forming the in-situ film (n=6) [21,22]. The method described by Darw hekar G et al; 2011 was used to determine the moisture content (MC) and moisture uptake by the film. Weighing a 2cm^2 area film and placing it in a desiccator with fused calcium chloride. The film was weighed again after 24 hours, and the moisture content was determined by using formula [17].

$$\%MC = \frac{W_{initial} - W_{final}}{W_{final}} \times 100$$

A moisture uptake was also performed out by placing precisely weighted film in a desiccator with a saturated potassium chloride solution for 24 hours at 84 percent relative humidity. The formula was used to determine the percentage of moisture uptake.

$$\%Moisture\ Uptake = \frac{W_{final} - W_{initial}}{W_{initial}} \times 100$$

1g FFH was added to PBS and vortexed for 10 minutes to determine drug content. The sample was centrifuged at 6000rpm for 10 minutes, the supernatant was collected, and the drug concentration was measured with a UV spectrophotometer at λmax 360nm [27]. The *in-situ* film was placed over the edge of the bottle with adhesive tape for the water vapour transmission (WVT) test, exposing area S to the fused calcium chloride available in the bottle. The bottle was then weighed and placed in a humidity chamber. The bottle was removed after 24 hours of exposure (T), reweighed (W), and WVT was determined using the equation [18].

$$WVT = \frac{W}{S \times T}$$

A stainless-steel ball was used in the rolling ball tack test. The ball was thrown from a slope into the created *in-situ* film, and the distance travelled by the ball was recorded, providing the tack measurement in inch [19].

The bio adhesive force was measured using a modified balance method on excised goatskin. The bio adhesive strength is determined by the mass (gm) required to remove the film. The balancing pans were removed. The right side was attached with a beaker and the left side with a glass slide using the strings. For balancing the assembly, a 20gm weight was also hang on the left side, and another glass slide was placed beneath the hanged slide. On both slides, the hairless goat skin was attached, 1gm of gel was put between these two goat skin faces, and a force was exerted to make a bond. The gel was then removed from the excised skin adhered by adding water to the beaker. The amount of water needed in the beaker is converted to mass, which is then given in gram as bio adhesive force [20].

In-Vitro drug Release Study

Using a Franz diffusion cell, an *in vitro* drug release study of the drug from *in situ* films of FFH was done. In short, the receptor compartment of the diffusion cell was filled with PBS 7.4 and the dialysis membrane was inserted between the acceptor and donor compartments. The diffusion cell was kept at 37°C and rotated at 50rpm. The sample was taken at a specified interval, analysed at λmax 360nm, and the cumulative drug release was calculated [21].

Different kinetic equations, such as zero-order cumulative percent release vs. time, first-order log percent drug remaining vs. time, and Higuchi percent cumulative drug release vs. square root of time [28], were used to determine the drug release kinetics.

Skin Irritation Study

The approval for conducting the skin irritation study was obtained from the Control and Supervision of Experiments on Animals, CPCSEA Committee (CPCSEA/IAEC/SGRRIT/2017-18/0264/PO/ReBi/2002). The albino Wistar rats weighing 100-120g were used. The experiment was conducted by the method as stated by Manish Kumar et al., 2019. First, the rat skin was shaved and washed with distilled water in triplicate. Then the gel was applied on the shaven skin of the rat after 30min, where the gel transformed into the film. After 24hrs study, the applied area was cleaned with distilled water and observed for possible signs of irritation such as inflammation and redness [22].

Statistical Analysis

All experiments were repeated three times, and the results were provided as mean ±SD. ANOVA was used for determining the significant difference between various groups at $p<0.05$.

RESULT AND DISCUSSION

Using HPMC as a film former and Carbopol 934P as a gelling agent, an *in-situ* film-forming hydrogel was successfully prepared. Li X et al., 2014 prepared HPC and carbomer 934 based FFH in the same way. Propylene glycol was initially utilised as a plasticizer and penetration enhancer, and its involvement in film formation, drug release, and permeation was also determined. The ethanol improved the polymer's solubility and evaporated on application, reducing the time required for film formation [16]. Various trails were performed to decide the concentration of HPMC and carbopol in the formation of film forming gel. In trails, the concentration of carbopol varying from 0.25 to 1.5% and the concentration of HPMC ranged from 2% to 6%. The data was given in table 2. However 0.25 to 1.5 percent Carbopol have better gelling efficiency, resulting in a transparent gel formation [23-25], while 6 percent HPMC formed an inert, non-greasy and uniform film also stated [26].

Characterization of FFH

The pH of all formulations ranged from 6.53±0.047 to 7.2±0.081, which is acceptable and within range, as indicated in table 3.As reported by H. Lambers et al; 2006, the prepared FFH was also considered as non-irritant, because pH of the formulation was same as the physiological pH of skin [27].

The observed viscosity for all the formulation was optimal and within the required range. The FF0 formulation prepared without propylene glycol revealed the lowest viscosity. Furthermore, the viscosity increased with the concentration of propylene glycol. The result was similar to the study conducted [28-29]. In another study, undertaken by R Safriani et al., 2017 revealed that higher viscosity causes lower consistency and thus decreases the spreadability [30].

Table 2: Selection of Gelling Agent and Film Forming Polymer for Preparation FFH

Trail no.	Carbopol (%)	HPMC (%)	Inference	Comment
Trail 1	0.25%	2	Not selected	Neither gel nor film is formed.
Trail 2	0.75	6	Not selected	Gel is not formed and sticky film is prepared.
Trail 3	1.5	2	Not selected	Gel is formed, film is not formed.
Trail 4	1	6	Not selected	Film is formed but not well in appearance.
Trail 5	1.5	3	Not selected	Sticky film is formed.
Trail 6	1.5	6	Selected	Desirable *in-situ* film is formed.

Table 3: Characterization of FFH

Formulation code	pH value (Mean±S.D)	viscosity(cp)	Spreadability(cm^2) (Mean±S.D)
FF0	6.02±0.081	1495.75	19.01±0.123
FF1	7.03±0.169	1766.5	18.51±0.37
FF2	6.66±0.124	1859.37	17.56±0.24
FF3	6.56±0.094	1923.37	16.58±0.28
FF4	7.16±0.169	2180.75	15.39±0.4117
FF5	6.53±0.047	2343.25	12.81±0.17

Moreover, the observed viscosity revealed shear-thinning behaviours of gel as a reduction in apparent viscosity of gel was observed on increasing the shear rate. The observation was correlated by Varma VN [31]. The shear-thinning behaviour of gel was more evident with increased concentration of the penetration enhancer and the spreadability study indicated that gel is effortlessly spreadable even with lower shear force with spreadability range of 7.83 to 18.51. Similar results were observed by R. Khullant et al., 2011 for developed emulgel with spreadability from 11 to 14, reported as good result [29]. All formulations found to have film formation in 5-7minutes. Similar results were also reported for PVA, PVP, HPMC E15LV and HPMC E5LV based FFH [32].

The prepared *in-situ* film was homogenous, semi-transparent, free of bubbles and consistent in weight and thickness (0.2±0.031 mm). When the concentration of penetration enhancers in the formulation was increased, the moisture content of the formulations was also increased. Lower MC was also observed in the *in-situ* film, ranging from 18.94±0.05 to 21.02±1.43%. The MC is acceptable because the lower value produced a stable, slightly dry and fragile film, which is required for better results. The result also conferred the work. Moreover, moisture uptake by the film was 12.32 ± 0.23 to 32.21 ± 0.17%, which helped to maintain the physical stability and integrity of the *in-situ* film and could aid drug release [33]. Lower moisture uptake can also decrease the bulkiness and risk

of microbial attack. Also, the water vapor transmission rate from the film was 9.15 ± 0.02 to 19.22 ± 0.07%, which indicates the worthy permeability characteristic and stability of the *in-situ* film [34].

Rolling ball tack test and bio adhesion test indicated that tack of the *in-situ* film was appropriate to adhere to the skin surface. Lower tack value indicated the good adhesive nature of the film, as reported by Minghetti. P et al., 1999. The bio adhesive force was enough for providing effective adhesion property to film for an extended period of time. The force found to increase with the concentration of propylene glycol and the results were analogous to observation reported for the transdermal patch [35]. The drug content in the film ranged from 84.4±0.30 to 94.5±0.32 which suggested homogeneous distribution of the drug within the gel matrix [16].

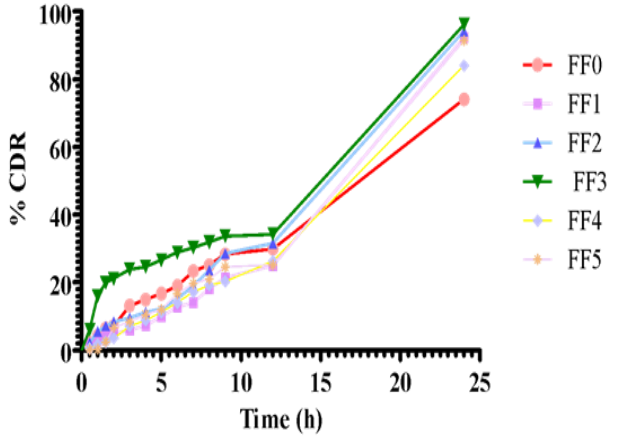
In-Vitro Drug Release Study

As shown in figure 1, maximum drug release was observed from FF2 while minimum with FF4. The order of the drug release FF0>FF4>FF5>FF1>FF2>FF3 with cumulative drug release of 74.02, 84.01, 91.36, 92.35, 94.35 and 96.23, % respectively. From the release study, it was observed that at 24h, the release was maximum with FF3, where cumulative drug release first increased with propylene glycol concentration (FF1 to FF3) and later decreased (FF4-FF5). Thus, increasing the concentration of propylene glycol can increase the drug release, for improving the dermal bioavailability also reported. The propylene glycol is also a highly hydrophilic humectant and thus can retain the moisture in the film, responsible for the higher drug release rate observed. Although, after a certain concentration, a decrease in cumulative release although the difference was not significant ($p<0.05$).

Table 4. Characterization of *In-Situ* Film

Formulation code	Weight uniformity(g m) (Mean±S.D)	Percent moisture content (Mean±S.D)	Percent moisture uptake (Mean±S.D)	Drug content (Mean±S.D)	Water vapour transmission (Mean±S.D)	Rolling ball tack test (in inches) (Mean±S.D)	Bio adhesion force (g) (Mean±S.D)
FF0	0.041±0.001	16.2±1.08	21.33±0.40	76.2±1.63	11.16±0.03	3.58±0.043	10.63±0.35
FF1	0.054±0.002	19.35±0.13	30.99±0.62	86.2±0.32	18.72±0.05	2.74±0.021	12.33±0.03
FF2	0.056±0.002	20.25±0.18	32.21±0.17	92.5±0.32	19.22±0.07	3.05±0.033	13.63±0.25
FF3	0.053±0.002	18.94±0.05	31.25±0.13	94.5±0.32	17.15±0.49	2.62±0.009	13.23±0.52
FF4	0.054±0.002	19.69±1.90	30.50±0.35	90.4±0.30	16.56±0.42	2.43±0.040	12.54±0.78
FF5	0.058±0.001	21.02±1.43	31.21±0.08	91.3±0.40	19.69±0.11	2.95±0.032	14.53±0.25

Figure 1: Effect of propylene glycol on *In-vitro* drug release profile of FF1 to FF5.



In-vitro Kinetic Study

In-vitro, drug release data were fitted to various kinetics models for determining the drug release kinetics and mechanism of drug release. Table 5 depicted that formulation FF1 to FF5 found to have a diverse r2 value with different kinetic models. Here, the best fit model was chosen on the basis of highest r2 value and the value n = 0.5 and 0.5 < n < 1.0 represents Fickian and non-Fickian diffusion, respectively while n = 1.0 follows super case II diffusion [40]. In the present study, super case II diffusion dominates over other drug release kinetics. But combining the kinetic study along with other evaluation studies. It was concluded that FF3 was the best formulation, following the Higuchi model and the Fickian diffusion. Hence, the drug release was found to be governed by a diffusion-controlled mechanism.

Table 5: Kinetic study of formulation FF1 to FF

Formulation code	r^2				n*	Best fit model	Mechanism of release
	Zero order	First order	Higuchi	Hixon crow			
FF1	0.9762	0.9633	0.8977	0.9680	1.6279	Zero order	Super Case II transport
FF2	0.9597	0.9460	0.8940	0.9512	0.8474	Zero order	Anomalous transport
FF3	0.7936	0.8419	0.9272	0.8203	0.5290	Higuchi	Fickian diffusion
FF4	0.9926	0.9932	0.8744	0.9932	1.1929	Hixon crow	Super Case II transport
FF5	0.9878	0.9898	0.8531	0.9895	1.6924	First order	Super Case II transport

Skin Irritation Study

The optimized formulation, FF3 was used for determining the FFH potential for causing skin irritation. The study provided a positive outcome, with no signs of any inflammation and redness. The study complies with the results reported for prepared hydrogel for dermal application [27]. Thus, prepared FFH was acceptable and

non-irritant to skin.

CONCLUSION

The amlodipine loaded *in-situ* film was successfully prepared by the solvent evaporation method, using a combination of carbopol 934 and HPMC E50LV where PEG 400 and glycerine were used as a plasticizer and propylene glycol as permeation enhancer. The effect of propylene glycol concentration on drug permeation was also evaluated which showed satisfactory results. The in vitro drug release study showed that propylene glycol improved drug release and permeation. FF3 was concluded as the optimized formulation and subjected to the skin irritation study. The non-irritant and better permeation of prepared *in-situ* FFH provided an effective drug delivery system with promising results and thus can be effectively used for topical application, bypassing the first-pass metabolism and thus increasing the drug bioavailability and patient compliance. Thus, prepared amlodipine loaded FFH can be used as an alternative to the conventional topical formulation for efficient drug delivery. Designed *in-situ* Film-forming hydrogel (FFH) can also be used for delivery of wound healing agents, antifungal drugs, drugs for skin melanoma, antihypertensive drugs, etc.

Conflict of Interest

All authors declare not to have any conflict of interest.

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