Original Article

Factors controlling development of benazepril mouth dissolving drug delivery system

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ABSTRACT

The objective of this trial was to design, formulate and *in vitro* evaluate benazepril hydrochloride (BNZH) (an anti-hypersensitive drug), fast dissolving oral film to deliver rapid onset of action as well as maximum therapeutic effectiveness through the simplicity of swallowing mainly for geriatrics who suffer from dysphagia. Different films were prepared via a solvent casting method sodium carboxymethyl cellulose (SCMC), hydroxyl propyl methyl cellulose (HPMC100), HPMC E15, and polyvinyl alcohol (PVA) as film developing polymers. Glycerin and propylene glycol (PG) was used as a plasticizer to improve the polymer film-forming characteristics. Tween 80 was used as a surfactant and citric acid (CA) as a saliva stimulating agent. Prepared films were then examined for both physical and mechanical properties including weight dissimilarity, thickness, surface pH, drug content as well as folding endurance. Both in vitro disintegration time in addition to drug release profile were also assessed for each formulation. According to the outcomes of this study, it is clear that F5 which consisted of 40% SCMC as a main film-forming polymer and 20% glycerin as a plasticizer, runs satisfactory physicochemical characteristics, *in vitro* DT (20 sec), nevertheless adequate release parameters as 99.8±0.14 released at 2 min and 80% of drug released in less than one minutes.

Keywords: Dysphagia, Disintegration, Fast dissolving, Geriatrics, Oral film

Introduction

Despite the fact of remarkable progress in the drug delivery system, oral administration of drugs is considered the furthermost preferred route on account of administration simplicity, non-invasiveness, flexibility, and patient compliance in addition to acceptability [1, 2]. Therefore numerous alternatives regarding administration through the oral route have continuously been presented by recent innovative technologies, mainly for pediatric in addition to geriatric, psychologically ill, and developmentally incapacitated patients since dysphagia is common in such groups [3, 4]. One such approach which has been arisen as innovative technology is fast dissolving oral film (FDOF) which considered the furthermost progressive form of orally administered solid dosage form [5]. FDOF can be distinct as a thin flexible film that rapidly wet, adhere, and dissolve to release the drug when located on the tongue or else in the buccal cavity due to the presence of hydrophilic polymers [6]. The great importance of FDOFs is raised from their distinctive characteristics and advantages which may include: swallowing simplicity for geriatrics, pediatrics as well as dysplasia patients who have tablets and capsules swelling difficulties, dosing accuracy, rapid once of action, improve bioavailability and stability [7, 8].

Benazepril hydrochloride (BNZH) is a non-sulfhydryl orally active angiotensin-converting enzyme inhibitor (ACE inhibitor) intended for the management of congestive heart failure, hypertension as well as prevention of nephropathy associated with diabetes mellitus [9, 10]. Blood vessel dilation is the main mechanism that consequences in the reduction of blood pressure. It is rapidly and partially absorbed afterward oral administration. Among the advantages of BNZH effectiveness and extended

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duration of action concurrently squat bioavailability is the main limitation [11].

Since the utmost of targeted group, is a candidate for swallowing problems that are related to age factors, BNZH sorts as a good nominee to be formulated as FDOF to enhance its oral bioavailability and increase patient compliance by the ease of swallowing.

Materials and Methods

Benazepril hydrochloride (BNZH) was purchased from Baoji Guokang Bio-Technology Co, Ltd, China. Sodium carboxy methyl cellulose (SCMC) low viscosity, hydroxypropylmethylcellulose 100 (HPMC100), sodium saccharine (Sod. Sach), and lactose were obtained from the Samara drug industry, Iraq. The citric acid (CA) was obtained from Panreac Quimica S.L.U., Barcelona. Polyvinyl acrylate (PVA), HPMC E15, and propylene glycol (PG) were purchased from Sinopharm Chemical Reagent Co, Ltd, China.

Preparation of fast dissolving film

Calculation

Diameter of petri dish =10 cm

The surface area of the petri dish =78.5 cm^2

Area of each film = 2×4 = 8 cm^2

Number of films = 78.5/ 8 =9.8 film approximately 10 film

Amount of drug in each casted petri dish = 10×20 = 200 mg

Formulation of fast dissolving oral film

The solvent casting technique was used to prepare seven formularies with dissimilar compositions as revealed in **(Table 1)**. The desired percentage of the polymer solution was prepared via the dispersion of the powder form of polymer into distilled water (DW) by persistent continuous stirring using a magnetic stirrer (Stuart, Copley scientific, and the U.K.). The resultant solution was then left without agitations for about 15 minutes (min) to eject the air bubble within the solution. An exactly weighed quantity of the drug, plasticizer as well as additional excipients was dissolved in DW separately. Once the complete hydration of the polymer with water was achieved, drug, plasticizer, and excipient solutions were added and mixed properly, and the volume was finalized with DW to 10 mL. The resulting solution was transferred into a well-defined surface area petri dish and then left to dry using an oven (Memmert, Germany) providing 40 °C. Finally, the resulting films were kept in aluminum foil.

Table 1. Complete content of each film

Ingredient (mg)	Formulas Code						
	F1	F2	F3	F4	F5	F6	F7
BNZH	20	20	20	20	20	20	20
SCMC	28	35		28	28		
HPMC 100			28				14
HPMC 15						28	
PVA							14
Glycerin	10	10	10		14	10	10
PG				10			
CA	1.4	1.4	1.4	1.4	1.4	1.4	1.4
Sod. Sach	0.6	0.6	0.6	0.6	0.6	0.6	0.6
Tween 80	2	2	2	2	2	2	2
Lactose	8	1	8	8	4	8	8

Evaluation of fast dissolving oral film

Visual Inspection

Different physical properties of all prepared FDOF for instance transparency, color, homogeneity as well as the surface of the oral films were assessed.

Weight variation

The assessment of weight variation of the FDOF was done by accurately weighting ten films separately by electrical balance (KERN, Germany) then the mean weight was calculated.

For the film to be counted on, the weight of not more than two FDOFs depart from the total average weight by no more than 7.5% in addition no film departs by more than 15%.

Thickness measurements

Five different points (center and four corners) were used to measure the thickness of each film using a Vernier caliper micrometer (Copley, UK.).

Folding endurance test

The folding endurance of randomly chosen films was discovered by repetitively folding one film at the same point until it cracks or reaches 250 folds maximum.

Surface pH

A combined pH meter (OHUS, USA) was used to determine the surface pH of the prepared films. The pH was measured by bringing the glass electrode in contact with the surface of the previously wetted oral film.

Disintegration time

A modified disintegration method was used to determine the disintegration time (DT). The film was carefully put in the midpoint of a petri dish full of 10 mL of water. The time intended for the film for complete disintegration to attenuated particles was recorded as disintegration time.

Drug content

Drug content evaluation was performed to determine the amount of BNZH present in the prepared films using the UV-Spectrophotometric technique using a UV-visible spectrophotometer (Shimadzu, Japan. In 100 mL of pH 6.8 phosphate buffer, an 8 cm^2 film was dissolved. The resultant solution was then filtered and absorbance was documented at 242.6 nm. The process was repetitive in triplicate and the mean was calculated.

In vitro dissolution study

In vitro dissolution study for the prepared film was performed using United State Pharmacopoeia (USP) dissolution apparatus type II (paddle apparatus) (Copley dissolution 8000, Copley scientific, UK.). The dissolution jars were filled with 500 ml of phosphate buffer pH 6.8 at 37 °C plus 50 rpm stirring speed.

For 60 min, a 5 mL sample of the solution is withdrawn at defined intervals and substituted with a fresh dissolution medium of similar volume. As a final point absorbance of these solutions was measured at 242.6 nm utilizing a Shimadzu UV/Vis double beam spectrophotometer.

Statistical analysis

The outcomes of the evaluation tests are specified as an average of triplicate samples ± standard deviation. One-way analysis of variance (ANOVA) was intended for statistical analysis. Significant statistical differences were considered when ($p < 0.05$).

Results and Discussion

Physicochemical properties of the prepared BNZH fast dissolving oral films

The organoleptic properties of all prepared films were assessed. All resultant films were homogeneous, flexible, and smooth. Films prepared with SCMC (F1, F2, F4, and F5) were found to be colorless and transparent while the ones prepared with HPMC (F3, F6, and F7) were white and non-transparent.

Average weights uniformity among the prepared formula with minor standard deviation were observed and all were within stated standards.

The thickness of prepared formulations was varying from 0.076± 0.03 to 0.089± 0.02 mm. The validity of the method of preparation can be assured by low values of standard deviation. Consequently, the employed preparation method can produce films with uniform thicknesses, causing uniformity in the content of BNZH to provide the desired does [12].

The pH of the surface of each prepared film was investigated to assess the side effects (mucosal irritation) associated with *in vivo* pH changes upon administration of inappropriate pH (acidic or else alkaline) formulation [13]. The surface pH range was from 5.5 to 7.4 which indicates that no mucosal irritation could produce from the prepared formulation.

Drug content for each film was assayed to assure even distribution of BNZH. A Uniform quantity of BNZH within the range of 85–115% (USP) was obtained which indicates the similarity of drug quantity in prepared films and signifies how very reproducible this method is [14].

results it is clear that all films have a pH value closer to the neutral pH, which indicates films do not cause any

Assessment of elasticity of prepared films was investigated to reveal their capacity to adapt to the site of administration. Discomfort, irritation, and loss of drug may result from breakage upon or even after application The elasticity was determined by measuring the capability of the film to endure rapture i.e. folding endurance [15]. All prepared films showed folding endurance values ranging from 240 to >300 which is considered conventional results. Physicochemical parameters of BNZH oral films are shown in **(Table 2)**.

Table 2. Physicochemical and release parameters of BNZH oral films

Formula Code	Weight (mg)	Thickness (mm)	Surface pH	Drug content (%)	Folding endurance	Disintegration time (s)	%D2	T80% min
F1	71 ± 2	0.08 ± 0.02	6.5 ± 0.1	101 ± 0.4	> 300	40	88.3±0.43	>1
F2	68 ± 1	0.088 ± 0.03	6.4 ± 0.2	100 ± 0.2	> 300	72	60.9±0.32	3.5 ±0.25
F3	72 ± 2	0.077 ± 0.02	7.2 ± 0.5	100 ± 0.2	270	120	37.9±0.4	5.5±0.25
F4	72 ± 3	0.09 ± 0.01	5.8 ± 0.2	95 ± 1	255	21	78.8±0.2	4±0.3
F5	73 ± 3	0.089 ± 0.02	7.4 ± 0.3	98 ± 0.3	> 300	20	99.8±0.14	>1
F6	72 ± 5	0.08 ± 0.03	5.5 ± 0.1	101 ± 2	240	63	49.8±0.34	4.5±0.55

F7	73 ± 1	0.076 ± 0.03	6.7 ± 0.3	98 ± 0.4	> 300	50	52.1±0.5	3.5±0.4

Formulation variables influencing features of prepared on BNZH oral films

Influence of polymer concentration on in vitro disintegration time and in vitro release profile of prepared film

therefore a 900 mL conventional disintegration tester won't be realistic nor represent the real environment

In vitro disintegration evaluation was implemented to confirm that drug release was from the dissolved film rather than from the intact film. To mimic the physiological conditions of the buccal cavity; small sublingual area and limited volume of saliva (not more than 6 mL), a modified procedure rather than the conventional one was employed to measure *in vitro* DT [16]. *In vitro* DT of prepared BNZH oral films is shown in **(Table 2)**.

Two formulas F1 and F2 which comprise different concentrations of SCMC (40% and 50%) respectively were used to study the influence of polymer concentration. The outcomes reviled that a significant rise in DT ($p<0.05$) was observed when SCMC concentration was increased (40 and 72 sec for F1 and F2 respectively). A longer DT may be attributed to a more viscous gel formed by the interaction between a film containing a higher polymer concentration and an aqueous medium [17].

Relating to *in vitro* drug release study, **(Table 2)** demonstrates the release parameters of all prepared formulations. Both the time required for 80 % of active ingredient to be released (T80%), as well as the percent of active ingredient dissolved in 2 min (% D2 min), were employed to determine *in vitro* release profile of the drug. Owing to the fast drug release in case of fast dissolving film formulations, the D2 min (percent drug dissolved in 2 min) was enrolled for assessment purposes [18].

From *in vitro* release parameter and as shown in **(Table 2)**, F2 (60.9±0.32) shows a significant reduction % D2 min ($p<0.05$) as well as shorter T80% (>1 min) in comparison to F1 (88.3±0.43), **(Figure 1)**. This could be related to the fact that the higher film forming polymer concentration, the more viscous gel layers formulation due to adjacent interaction among the particles of SCMC. Consequently reducing the drug particles' movement in swollen lattices and hence prods a drop-in rate of dissolution [19].

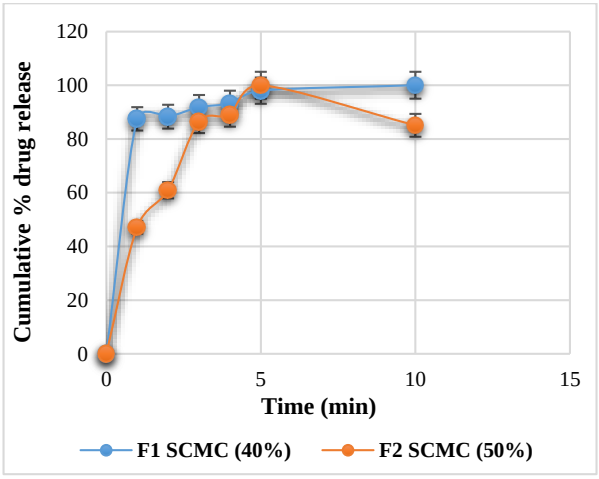

Figure 1. Influence of polymer concentration on dissolution behavior of prepared films

Influence of polymer type on in vitro disintegration time and in vitro release profile of prepared film

Effect of polymer type studied by substituting SCMC in F1 with the same concentration (14.3%) of HPMC100 in F3. A significant increase in DT ($p<0.05$) was observed, as shown in **(Table 2)**. Faster disintegration of F1 (40 sec) in comparison to F3 (120 sec) may be owing to differences in polymer nature. SCMC is more hydrophilic compared to HPMC100. Consequently higher solubility in an aqueous medium and rapid matrix disintegration [20].

In vitro release study reviled a significant decrease ($p<0.05$) in % D2 of F 3 (37.9±0.4) and longer T80% (5.5±0.25 min) compared to F1 (88.3±0.43) and as shown in **(Table 2)** and **(Figure 2)**. This outcome may be justified by differences in viscosities of the gel formed by each polymer upon hydration with an aqueous medium in consequence of differences in polymer nature [21].

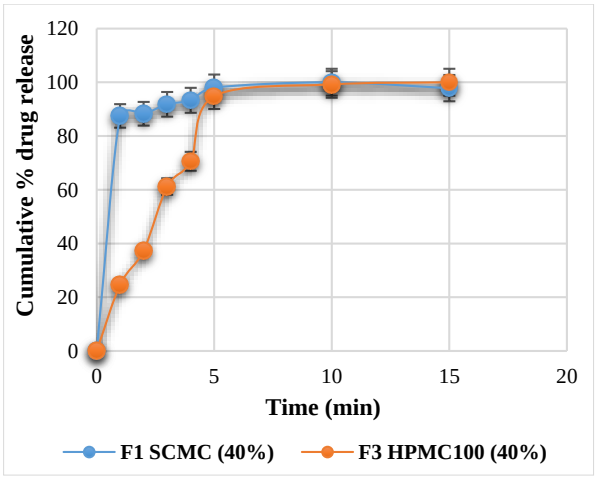

Figure 2. Influence of polymer type on dissolution behavior of prepared films

Influence of plasticizer type on in vitro disintegration time and in vitro release profile of prepared film

The influence of plasticizer type was studied using F1 and F4 which contain the same concentration (14.3%) of glycerin and PG respectively.

Results reviled non significance decrease in DT ($p>0.05$) for F4 (20 sec) compared to F1 (40 sec). This may be related to the point that both plasticizers act by enhancement of medium diffusion into the film, alteration in the density of SCMC packed chain thus causing less dense and more porous structure that breakdowns by reduced force and hasten film disintegration [22, 23].

The outcomes of *in vitro* drug release revealed longer T80% (4±0.3 min) as well as a non-significant decrease ($p>0.05$) in % D2 of F4 (78.8±0.2) related to F1 (88.3±0.43), as shown in **(Table 2)** and **(Figure 3)**. This may be justified by the fact that both glycerin and PG are soluble in water and they will disperse out from the films in an aqueous medium creating void spaces in the oral film by which distribution of liquid occurs to permit film disintegration resulting in improved release profile of drug [19, 24].

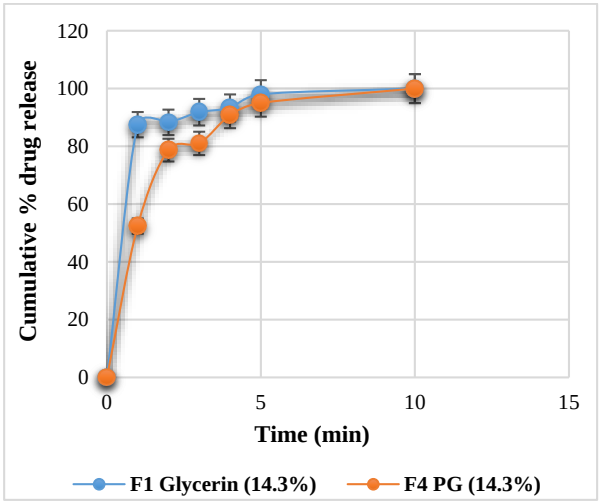

Figure 3. Influence of plasticizer type on dissolution behavior of prepared films.

Influence of plasticizer concentration on in vitro disintegration time and in vitro release profile of prepared film

Both F1 and F5 which contain 14.3% and 20% glycerin respectively were employed to study the effect of plasticizer concentration.

The results display that increasing glycerin concentration as shown in F1 and F5 has a non-significant decrease in DT ($p>0.05$). This may be attributed to the hygroscopic nature of glycerin, a higher concentration of glycerin resulted in a surging hydrophilic feature of film and thus extended the inner space of polymer molecular structure [25, 26].

On the other hand significant increase ($p<0.05$) in % D2 was observed when the concentration of glycerin increased was %D2 value was 99.8±0.14 and 88.3±0.43 for F5 and F1 respectively, as shown in **(Table 2)** and **(Figure 4)**. This outcome could be related to the performance of glycerin as a dissolution expediting agent as well as its hydrophilic nature, therefore higher glycerin concentration will rise the drug release rate [27, 28].

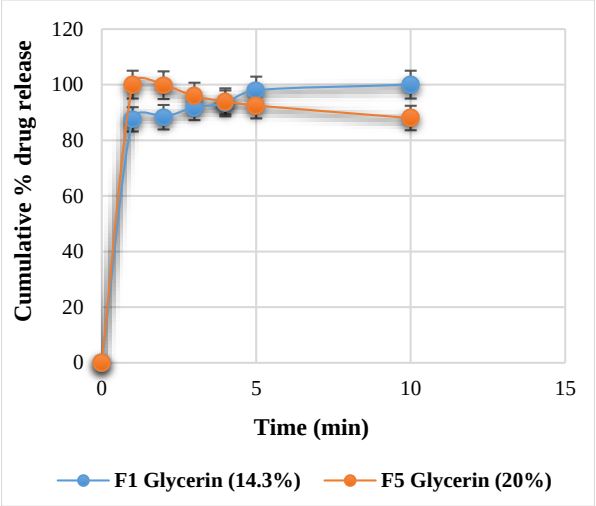

Figure 4. Influence of plasticizer concentration on dissolution behavior of prepared films.

Influence of polymer grade on in vitro disintegration time and in vitro release profile of prepared film

The effect of polymer grades was studied using F3 and F6 which contain 40% of HPMC100 and HPMC15 respectively.

A significant decrease ($p<0.05$) in DT was observed as the grade of HPMC decreased as the DT was 120 and 60 sec for F3 and F6 correspondingly. Reduction in DT may be related to higher gel viscosity which impacts the time required for the film to fragment [29].

Shorter T80% (4.5±0.55 min) and significant increase ($p<0.05$) in % D2 was observed when HPMC100 was substituted by HPMC15, as shown in **(Table 2)** and **(Figure 5)** where % D2 for F3 and F6 was 37.9±0.4 and 49.8±0.34 correspondingly**.** This result could be explained by differences in viscosity grade of HPMC resulting from differences in molecular weights. Consequently, hydration with an aqueous medium polymer with higher molecular weight produces thicker gel layers with a longer diffusion path reducing drug effective diffusion hence a drug release rate drop [30, 31].

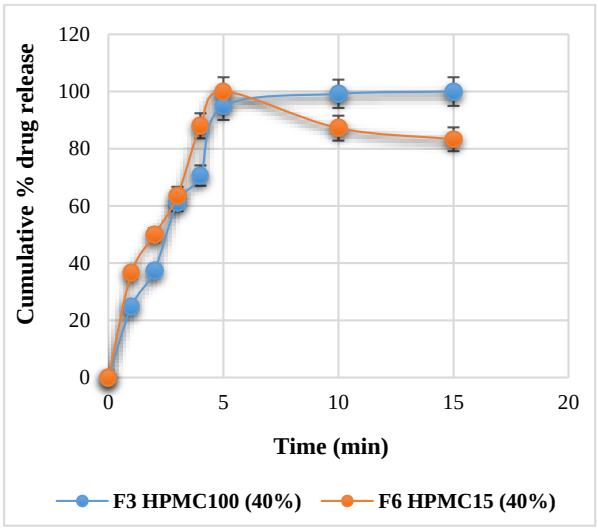

Figure 5. Influence of polymer grade on dissolution behavior of prepared films

Influence of polymer blend on in vitro disintegration time and in vitro release profile of prepared film

The impact of polymer combination was studied utilizing F3 and F7 which contain 40% of HPMC100 and polymer combination (HPMC100: PVA) in the ratio (1:1) respectively.

The DT was reduced significantly ($p<0.05$) when the polymer mixture is used as it was 120 and 50 sec for F3 and F7 respectively. This may be accredited to water penetration into film assembly in a formula containing PVA as a result of the higher aqueous solubility of PVA compared to HPMC100, leading to reduced DT [31].

The *in vitro* release parameters as shown in **(Table 2)** and revealed that the incorporation of PVA into HPMC100 polymeric oral dissolving film in a ratio of (1:1) resulted in a significant increase in % D2 in F7 52.1±0.5 compared to F3 37.9±0.4. This is may result from erosion of loosely bounded PVA molecules due to high PVA solubility in an aqueous medium [23].

Conclusion

Conferring to the outcomes obtained; Formula (F5) which contains 40% (w/w) SCMC as a film-forming polymer, 20% (w/w) glycerin as a plasticizer, and tween80 as surfactants is stared as an optimized formula since it presented improved physic-mechanical characteristics of the OFDFs as well as low DT (20 ± 6 sec). The formula also shows % D2 (99.8±0.14) and 80% of drugs released in less than 1 min.

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