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Original Article

DESIGN AND EVALUATION OF FAST DISSOLVING ORO-DISPERSIBLE FILMS OF METOCLOPRAMIDE HYDROCHLORIDE USING 3^2 MULTIFACTORIAL DESIGNS

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ABSTRACT

Objective: The objective of the present work was to develop and optimize fast dissolving orodispersible films containing metoclopramide hydrochloride using 3^2 multifactorial designs.

Methods: The films were prepared by solvent casting method using hydroxypropyl methyl cellulose E5 (HPMC E5) and sodium starch glycolate (SSG) as two independent variables in three levels in concentration 2.5, 3, 3.5% w/wand 1, 1.5, and 2 % respectively. The percent of *in vitro* drug release (Y_1) and the disintegration time (Y_2) were chosen and studied as dependent responses. The prepared films were also evaluated for their weight uniformity, thickness, surface pH, drug content, *in vitro* disintegration time, *in vitro* drug release, film stability and mechanical properties as folding endurance.

Results: All the films were transparent. The films weight (mg) was ranging from 63±0.78 to 86±0.82 while the film thickness (mm) and the folding endurance range from 0.22±0.53, 50±0.58 to 0.32±0.35 and 90±0.84 respectively. The drug content (mg %) was studied, and it ranges from 98.24±1.08 to 99.07±1.02. It was found that the relative standard deviation (% RSD) met the criteria of USP specification for drug content (>6%). *In vitro* disintegration time was tested; all films satisfied the requirement of disintegration time for fast dissolving dosage form (<1 min), it ranged from 2.24±1.75 to 3.18±1.87 sec. The stability studies revealed no significant differences before and after storage for the all formulations.

Conclusion: An optimized metoclopramide HCl film was achieved that could be a benefit to a patient suffering from emesis, in which hydroxypropyl methylcellulose (E5) was used as a film forming polymer in its high level (3.5%) in addition to sodium starch glycolate in its high level (2%).

Keywords: Fast dissolving orodispersible films, Optimization, Metoclopramide HCL, 3^2multifactorial designs

INTRODUCTION

A fast dissolving oral film (FDF) has been successfully used to deliver medicines to patients having difficulty in swallowing, those with oral pain due to mucositis or after oral surgery, or those with nausea. Several film preparations have been developed for analgesics such as ketrolac [1] or fentanyl [2, 3], the antiemetic agent prochlorperazine [4] and Ca2+channel antagonist verapamil [5].

Fast-dissolving oral delivery systems are solid dosage forms, which disintegrate or dissolve within 1 min when placed in the mouth without drinking or chewing [6].

The first developed fast-dissolving dosage form consisted in tablet form, and the rapid disintegrating properties were obtained through a special process or formulation modifications [7]. More recently, fast-dissolving films are gaining interest as an alternative to fast-dissolving tablets to eliminate definitely patients' fear of choking and overcome patent impediments. Fast-dissolving films are generally constituted of plasticized hydrocolloids or blends made of them that can be laminated by solvent casting or hot-melt extrusion [8].

Common problems are caused by foaming during the film formation due to the heating of the material or solvent evaporation, the flaking during the slitting and the cracking in the cutting phase. Furthermore, the films should be stable to moisture over time. Finally, to facilitate the handling they have to be flexible and exhibit a suitable tensile stress and do not stick to the packaging materials and fingers.

Metoclopramide was chosen as a model drug, the drug selection based on a high frequency of prescribing, an appropriate indication and the age for this new dosage form.

Metoclopramide hydrochloride is a white crystalline, odorless substance, and its freely soluble in water. It is used as an anti-emetic in the treatment of some forms of nausea and vomiting associated with cancer therapy, pregnancy, migraine, etc., and to increase gastrointestinal motility [9]. However the oral bioavailability of metoclopramide HCl is highly variable showing values between 32 and 98 % due to expensive pre-systemic metabolism [10, 11]. This work aims to formulate, design and optimize fast dissolving orodispersible films of metoclopramide HCL at various concentration of film-forming polymer (HPMC E5) and super-disintegrant (sodium starch glycolate) by using3^2 multi-factorial design and to evaluate their influence on the percent of *in vitro* drug release and the disintegration time.

MATERIALS AND METHODS

Materials

Metoclopramide Hydrochloride, hydroxypropyl methylcellulose (HPMC), and sodium starch glycolate (SSG) were obtained as gift sample by Sedico for Pharmaceuticals (6 of October, Giza, Egypt). Other chemicals were purchased from ADWEC, Egypt and they were of analytical grade.

Preliminary trials

Selection of polymer

Different grades of HPMC (k4m and E5) were tried for the preparation of fast dissolving orodispersible films (FDF). HPMC k4m did not show a good result, the film was not easily peelable, sticky in nature and did not give good films.

HPMC E5 was selected for the formulation of films as it forms good easily peelable and non-sticky films.

Preparation of the films

The fast dissolving films were prepared by a solvent casting method. The required percentage of polymer solution (HPMC E5) (2.5, 3, and

3.5% w/w) was prepared by dispersing the polymer powder in distilled water with continuous stirring at 70 °C. After continuous stirring the solution was left undisturbed for five to eight hours to remove all the air bubbles. Accurately weighed quantity of drug, plasticizer and all other excipients was separately dissolved in distilled water in another beaker. After complete hydration of the polymer with water, drug-plasticizer and all other excipient solutions were added and mixed thoroughly, and the volume was made up 30 milliliters with distilled water. The polymeric solutions were then poured on the mold, allowed to dry at 45 °C. The resultant films were cut into the dimension of 2x2 cm^2 in size in which 10 mg of metoclopramide hydrochloride was included [5, 12]. The prepared films are packed immediately after the reparation in individual airtight aluminum seal packs and stored at 25 °C until use.

Experimental design and statistical analysis

A 3^2-factor, 3-level factorial design was used to explore response surfaces and constructing second-order polynomial models with statgraphic plus software (Version 4.1). The 3-level factorial design was specifically selected since it requires fewer runs than other experimental designs. The nonlinear computer, generated quadratic model is given as (equation 1): $Y=\beta 0+\beta_1 X_1+\beta_2 X_2+\beta_{12} X_1X_2+\beta_{11} X_1^2+\beta_{22} X_2^2$

Where Y is the predicted response (dependent variable); β_0 is the model constant (arithmetic mean response); $X_1$and X_2 are the independent variables and represent the average result of changing one factor at a time from its low value to the higher one; The terms X_1X_2 represent the changes of response when the two factors are simultaneously changed; The terms X_1X_1 and X_2X_2 are used to indicate non linearity; β1 and β2 are the linear coefficients; β12 are the cross-product coefficient; and β11, and β22 are the quadratic coefficients. 3-level design, where selected each variable is tested at a low (-1), medium (0) and high (+1) level. The percent of *in vitro* drug release (Y_1) and the disintegration time (Y_2) were chosen and studied as dependent responses. Nine Metoclopramide hydrochloride FDF formulations were prepared according to 3^2full factorial designs to optimize the formulation factors and evaluate the main effects. The independent variables were the polymer % (HPMC E5) (X_1) and superdisintegrant % (SSG) (X_2). Three levels of HPMC E5 % were used 2.5, 3 and 3.5%, denoted the value-1, 0 and 1in the above design respectively.

Three levels of SSG concentration were chosen to be 1 %, 1.5 % and 2 % denoted-1, 0 and 1 respectively are represented in table 1. The nine experimental trials and the respective observed responses are given in table 2.

Table 1: Independent variables and the selected levels for metoclopramide oro-dispersible film formulations

Factor	Low(-1)	Medium (0)	High(1)
X1 (HPMC E5 % w/w)	2.5	3	3.5
X2 (SSG % w/w)	1	1.5	2

Table 2: Variables and observed response in 3^2 factorial design of metoclopramide orodispersible film formulations

Formulation	Independent variables		Dependent variables			
			Predicted values		observed values	
	X_1	X_2	Y_1	Y_2	Y_1	Y_2
F1	-1	0	93.57±2.12	3.00±1.30	94.16	2.76
F2	1	-1	94.62±3.74	2.57±2.20	94.28	2.89
F3	0	1	92.76±1.72	3.10±3.05	92.50	3.01
F4	1	-1	90.32±2.05	2.24±1.75	90.04	2.14
F5	0	1	93.213.21	2.45±0.98	92.89	2.40
F6	-1	0	90.75±1.75	2.50±0.53	94.28	2.37
F7	1	-1	93.21±3.08	3.00±1.75	92.05	3.06
F8	0	1	95.32±0.52	3.18±1.87	96.80	2.90
F9	1	-1	100.00±0.56	2.52±2.00	98.82	2.73

X1= % w/w of polymer (hydroxpropylmethyl cellulose-HPMC E5), X2=% w/w of superdisintegrant (sodium starch glycolate-SSG), Y1= % of *in vitro* drug release, Y2= disintegration time (sec)

Table 3: Composition and codes of metoclopramide orodispersible film formulations

Components	Formula code								
	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
Metoclopramide (g)	0.65	0.65	0.65	0.65	0.65	0.65	0.65	0.65	0.65
HPMC E5*(g)	2.5	3	3.5	2.5	3	3.5	2.5	3	3.5
SSG*(g)	1	1	1	1.5	1.5	1.5	2	2	2
Glycerol (ml)	2	2	2	2	2	2	2	2	2
Citric acid (g)	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Mannitol (g)	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04
Aspartame (g)	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04
Purified water(ml) to	100	100	100	100	100	100	100	100	100

*HPMC E5: Hydroxypropyl methylcellulose E5, * SSG: Sodium starch glycolate

Physical appearance of the film

Appearances of the films such as transparent or opaque were evaluated by visual observation [8, 13].

Weight uniformity of the film

The weight of film strip (2x2 cm) of metoclopramide hydrochloride was determined by an analytical balance (Shimazdu, Japan) [8]. Experiments were carried out in triplicates.

Thickness of the film

Film thickness was measured by means of a micrometer (precision± 0.0001 mm Mitutoyo Corporation, Japan). The thickness of each film was measured at three different positions of the film and the average thickness was calculated [5]. Experiments were carried out in triplicates.

Folding endurance study

It was measured manually for the prepared fast dissolving film (2 X 2 cm). A strip was repeatedly folded at the same place till it broke. The number of times the film could be folded at the same place without breaking gave the value of folding endurance. This test was performed on three films of each formulation [14].

Surface pH

The surface pH of fast dissolving strip was determined in order to investigate the possibility of any side effects *in vivo*. As an acidic or alkaline pH may cause irritation to the oral mucosa, it was determined to keep the surface pH as close to neutral as possible. A combined pH electrode was used for this purpose. Oral strip was slightly wet with the help of water. The pH was measured by bringing the electrode in contact with the surface of the oral film (Orion Research, Inc., USA). This study was performed on three films of each formulation [15].

Drug content determination

The content uniformity of each oral film was tested for metoclopramide HCl using UV spectroscopy at 273 nm. One fast-dissolving film of 2 cm x 2 cm was selected and dissolved in 100 ml of phosphate buffer pH 6.8 then the concentration of the drug was determined from a previously constructed standard calibration curve. According to the USP standards, the contents of preparations should lay between the limits 98 to 101%. The results were expressed as mean of three determinations of each formulation [16].

***In vitro* disintegration studies**

Disintegration time gives an indication about the disintegration characteristics and dissolution characteristics of the film. The film as per the dimensions (2 x 2 cm) required for dose delivery was placed on a stainless steel wire mesh placed in a petri dish containing 10 ml phosphate buffer pH 6.8 at 37 °C. Time required for the film to break was noted as *in vitro* disintegration time. This test was performed on three films of each formulation [17, 18].

***In vitro* drug release**

The *in vitro* dissolution test of metoclopramide HCl films was performed three times using (900 ml; phosphate buffer pH 6.8 with USP paddle dissolution apparatus II (Hanson SR8-plus 80, USA) at 50 rpm and 37±0.5 °C temperature. The drug release was analyzed spectrophotometrically at λ max 273 nm using ultraviolet (UV) spectrophotometer by using a previously prepared calibration. One film was placed into each vessel and test sample (5 ml) was withdrawn at particular time interval (10, 20, 30, 40, 60 and 90 Seconds) and replaced with fresh dissolution media maintained at 37±0.5 °C. In order to prevent the film strips from floating, each strip was fixed to a glass slab and placed at the bottom of the dissolution vessel before starting the dissolution test [19].

Accelerated stability studies

The prepared films were packed and subjected to stability studies at 40 °C/75 % relative humidity (RH) for a period of 3 mo. Samples were withdrawn at time intervals of 15 d and evaluated for physical parameters, pH, drug content, and drug release [20].

RESULTS AND DISCUSSION

Characterization of fast dissolving films

Metoclopramide orodispersible films prepared were transparent, colorless, thin and with no spots on the film surface. The prepared film was evaluated for the following parameters: Physical Appearance of the film, weight uniformity of the film, the thickness of the film, folding endurance study, surface pH, drug content determination and *in vitro* disintegration studies as shown below in table 4.

All the films were transparent. The films weight (mg) was ranging from 63± 0.78 to 86± 0.82 while the film thickness (mm) and the folding endurance range from 0.22±0.53, 50±0.58 to 0.32±0.35 and 90±0.84 respectively. The drug content (mg %) was studied and it range from 98.24± 1.08 to 99.07±1.02. It was found that the relative standard deviation (% RSD) met the criteria of USP specification for drug content (>6%) [21].

In vitro disintegration time was tested; all films satisfied the requirement of disintegration time for fast dissolving dosage form (<1 min), it ranged from 2.24±1.75-3.18±1.87 sec.

Table 4: Physical appearance, weight uniformity, thickness, folding endurance, pH, and drug content and *in vitro* disintegration of metoclopramide films

Formulations	Physical appearance	Weight uniformity[a]	Thickness (mm)[a]	Folding endurance[a]	pH[a]	Drug content (mg %)[a]	*In vitro* disintegration (sec)[a]
F1	Transparent	66.00±0.23	0.24±0.5	50±0.58	6.80±0.2	98.81±1.17	3.00±1.30
F2	Transparent	76.00±0.56	0.23±0.14	58±0.47	6.90±2.4	98.24±1.08	2.57±2.20
F3	Transparent	63.00±0.78	0.31±0.81	60±0.59	7.05±1.4	99.05±1.51	3.10±3.05
F4	Transparent	76.00±1.25	0.32±0.35	60±1.44	7.08±0.8	99.47±0.68	2.24±1.75
F5	Transparent	63.00±3.01	0.28±0.42	64±1.12	6.94±1.7	98.84±0.73	2.45±0.98
F6	Transparent	76.00±2.73	0.24±0.14	67±0.64	6.85±1.1	98.39±0.71	2.50±0.53
F7	Transparent	70.00±2.10	0.22±0.53	80±1.04	6.91±1.0	98.47±1.31	3.00±1.75
F8	Transparent	86.00±0.82	0.30±0.81	82±1.01	6.87±0.8	98.64±1.24	3.18±1.87
F9	Transparent	75.00±0.75	0.27±0.24	90±0.84	7.08±0.5	99.07±1.02	2.52±2.00

[a]mean±SD, *n=3*.

***In vitro* drug release**

The *in vitro* drug release of different films was investigated and the results are represented in fig. 1. The release of metoclopramide from its film can be ranked in the following descending order: F9>F4>F8>F2>F5=F7>F1>F3>F6 where the amount of drug release after 30 min was found to be 100%, 97.3%, 95.32%, 94.62 %, 93.21%, 93.57%, 92.76% and 90.75%, respectively.

Formulations F9 was observed to have the highest release, this was due to the presence of the highest concentration of water soluble hydrophilic polymers (HPMC E5 3.5%) which dissolves rapidly and introduce porosity. The void volume is thus expected to be occupied by the external solvent which diffuses into the film and thereby accelerate dissolution. Also the presence of SSG (2%) which act as super disintegrant increase the rate of film disintegration. The results of metoclopramide films are in agreement with Raju et al., [22], who showed that the presence of highest concentration of water soluble hydrophilic polymers (HPMC E5) increases the release from the prepared films. Also the increase in the amount of hydrophilic carrier leads to the increase in the wettability and dispersibility of the drug from the film resulting in the dissolution of the film. [23] This result is matched with that observed in the enhancement of dissolution of fenofibrate. [24]

Optimization of formulation using 3^2 multifactorial designs

Nine metoclopramide hydrochloride FDF formulations were prepared according to 3^2full factorial designs to optimize the formulation factors and evaluate the main effects. The independent

variables were the polymer percent (HPMC E5) (X_1) and super disintegrant percent (SSG) (X_2). Three levels of HPMC E5 percent were used 2.5, 3 and 3.5%, denoted the value-1, 0 and 1in the above design respectively.

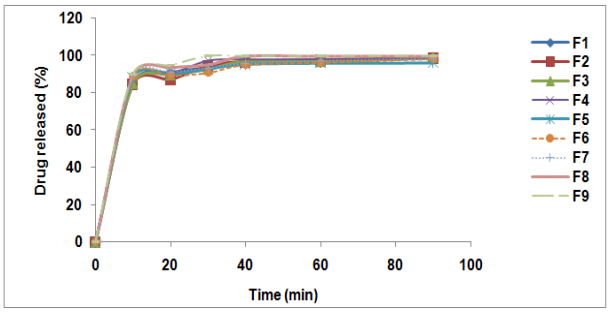

Fig. 1: *In vitro* drug release of fast dissolving orodispersible films (F1-F9)

Three–dimensional (3D) plots and standard pareto chart for the percent of *in vitro* drug release (Y_1) and the disintegration time (Y_2) were chosen and studied as dependent responses and were drawn using stat graphics plus design software (version 4.1) is shown in fig. 2-3 respectively.

Contour plots were prepared for all the three responses Y_1, Y_2 andY_3 are shown in fig 8-10 c. These plots are used to study the interaction effects i.e. the effects of two factors at one time. The observed and the predicted values were shown in table 2 while the R-squared values were represented in table 5.

The response Y_1 which is the percent of *in vitro* drug release is represented by the following polynomial equation (equation 2):

$$Y_1 = 113.29 + 13.49\ X_1 - 62.11\ X_2 - 3.79\ X_1^2 + 7.6 X_1 X_2 + 13.94\ X_2^2$$

Where, Y_1 is the percent of *in vitro* drug release, X_1 is the polymer percent, and X_2 is the superdisintegrant percent. The polynomial equation was generated by multiple linear regressions. The percent of *in vitro* drug releasevalues are dependent on the selected independent variables. The fitted equation relates the response (the percent of *in vitro* drug release) to the transformed factor as shown by equation 2. The results of regression analysis revealed that on increasing the value of X_1, the percent of *in vitro* drug release increases and this is observed by the positive sign coefficient of β_1 (the linear coefficient). While the percent of *in vitro* drug release was noticed to be decreased as the values of X_2 increase, this was noticed by the negative sign of β_2 (the linear coefficient).

The response Y_2 which is the disintegration timeis represented by the following polynomial equation (equation 3):

$$Y_2 = 248.46 + 59.4\ X_1 - 254.8\ X_2 - 1.6\ X_1^2 - 34.8 X_1 X_2 + 119.6\ X_2^2$$

The fitted equation relates the response (the disintegration time) to the transformed factor as shown by equation 2. The results of regression analysis revealed that on increasing the value of X_1, the disintegration time increases and this is observed by the positive sign coefficient β_1 (the linear coefficient). While the disintegration time was noticed to be decreased as the values of X_2 increase, this was noticed by the negative sign of β_1 (the linear coefficient).

Regression analysis of the data was carried out in statistical analysis system (SAS) by a special cubic model. From ANOVA study on the data of the percent of *in vitro* drug release (Y_1) and the disintegration time (Y_2) is shown in table 5, the standard error was below 5%, indicating that the observed responses were very close to predicted values. The Durbin-Watson (DW) statistic tests the residual to determine if there is any significant correlation between data, since the DW value is greater than 1.4, there is probably not any serious autocorrelation in the residuals.

The promising formulation was selected on the basis of the accepted criteria of percent of *in vitro* drug release (Y_1) anddisintegration time (Y_2). From the obtained results, hydroxypropyl methyl cellulose (E5) as a film forming polymer was used inits high level (3.5%) in addition to sodium starch glycolate in its high level (2%). These criteria were found in formulation F9 as the observed values were very close to the predicted ones as shown in table 6.

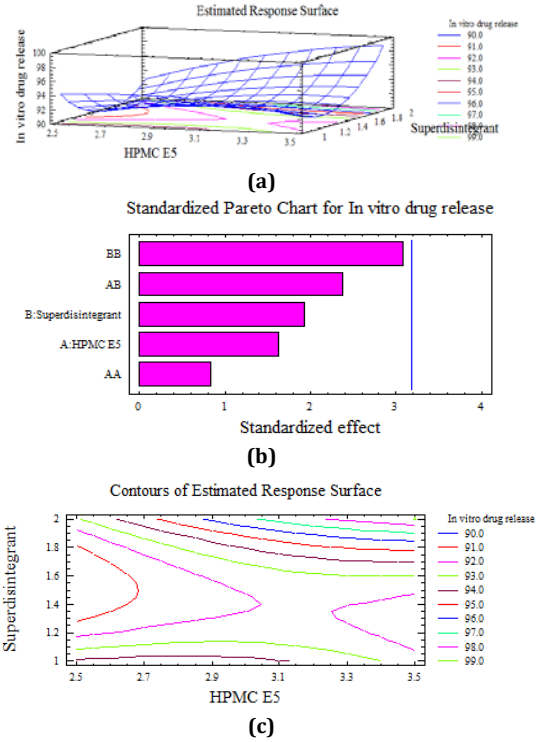

Fig. 2: (2. a) Response surface plot, (2. b) Standard pareto chart and, (2. c) contour plot showing the effect of X1 and X2 on the drug release after 30 min. (Y1)

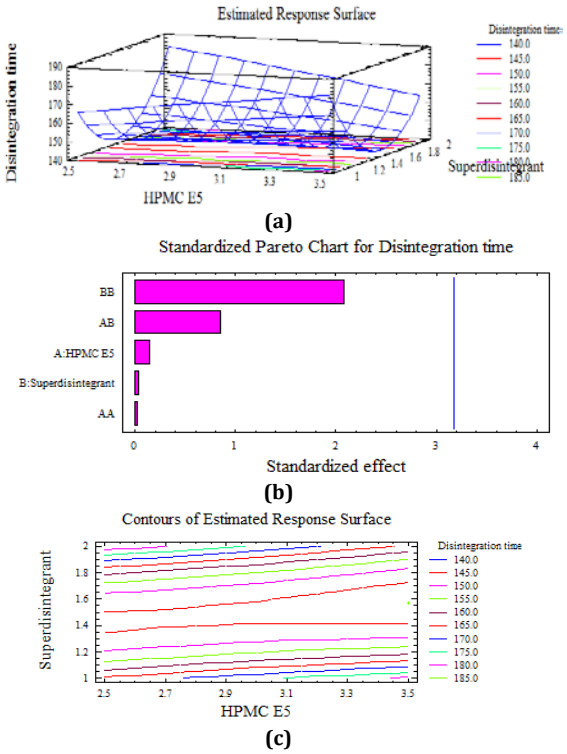

Fig. 3: (3. a) Response surface plot, fig. (3. b) standard pareto chart and fig. (3. c) contour plot showing the effect of X1 and X2 on disintegration time (Y2)

Table 5: Summary of results of regression analysis for responses Y_1 (percent of *in vitro* drug release) and Y_2 (disintegration time)

Response	R^2	Adjusted R^2	Standard error	Mean absolute error	Durbin-Watson statistic
In vitro drug release	88.137	68.366	1.598	0.780	2.040
(Y_1) Disintegration time (Y_2)	62.983	1.289	20.284	10.359	2.415

Table 6: Observed and predicted values of the responses for the optimized metoclopramide Fast dissolving orodispersible Film (F9)

Response	Observed value	Predicted value	Residual
In vitro drug release (Y_1)	100	98.82	-1.18
Disintegration time (Y_2)	151.2	163.96	12.76

Stability study

After subjecting all formulations to stability studies at 40 °C/75 % relative humidity (RH) for a period of 3 mo, samples were withdrawn at time intervals of 15 d and evaluated for physical parameters, pH, drug content, and drug release. The stability studies revealed no significant differences before and after storage for the all formulations.

CONCLUSION

The main aims and objective of the present study was to formulate, design and optimize fast dissolving oro-dispersible films of metoclopramide HCL at various concentration of film forming polymer (HPMC E5) and superdisintegrant (sodium starch glycolate) by using 3^2 multi factorial design and to evaluate their influence on the percent of *in vitro* drug release and the disintegration time. The films were prepared using solvent casting method using HPMC as polymer and SSG as a super disintegrant. HPMC was selected as the polymer used for their matrix forming properties while sodium starch glycolate (SSG) is used for its super disintegrant effect. The study shows that the use of 3^2factorial designs are valid in predicting the optimized formulation which was found in formulation F9 as the observed values were very close to the predicted ones, and in which hydroxypropyl methyl cellulose (E5) was used as a film forming polymer in its high level (3.5%) in addition to sodium starch glycolate in its high level (2%). The stability studies revealed no significant differences before and after storage for the selected formula.

CONFLICTS OF INTERESTS

All authors have none to declare.

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