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Research Article

Formulation and Evaluation of Floating Mucoadhesive Tablet of Clopidogrel

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ABSTRACT
The objective of the present study was to formulate and evaluate Floating Mucoadhesive tablets of Clopidogrel for the treatment of antithrombotic and antiplatelet agent. Tablets were prepared by direct compression using directly compressible polymers such as HPMC K4M, and Carbopol 934 were evaluated for drug-excipient compatibility, density, buoyancy test, mucoadhesion force, swelling study, drug content and *In-Vitro* release profile. Sodium bicarbonate and citric acid were used producing effervescent base for buoyancy of tablets. Analysis of drug release from tablet indicates drug release by zero order, first order rate kinetics. No significant change was observed in physical appearance, drug content, floatability or in-vitro dissolution pattern after storage at 45^0C/75^0C RH for three months.

Keywords: Floating Mucoadhesive tablet, GIT, Clopidogrel, HPMC K4M, Carbopol 934.

INTRODUCTION

Oral drug administration still remains the route of choice for the majority of clinical applications some drug have ideal characteristics for good absorption to occur desirable for optimizing the therapeutic benefit of the drug[1]. Oral delivery of drugs is by far the most preferable route of drug delivery due to the ease of administration, patient compliance and flexibility in formulation[2]. Attempts have been made to be 8-10 hr. From mouth to colon, is relatively brief with considerable fluctuation. One of the important determinants of G.I transit is the residence time in the stomach. The oral controlled delivery of drugs having "absorption window" continually releasing the drug prior to absorption window for prolonged period of time, thus ensuring optimal bioavailability[3]. A floating dosage unit is useful for drugs acting locally in the proximal gastrointestinal tract. These systems are also useful for drugs that are poorly soluble or unstable in intestinal fluids. Floating tablets and Floating capsules are common examples of floating system[4,5].

Floating Mucoadhesive Drug Delivery System

A gastro retentive dosage form will release the drug over an extended period in the stomach and upper gastrointestinal tract (GIT) thus enhancing the opportunity for absorption. Various approaches have been proposed to control the gastric residence of drug delivery system in the upper part of the GIT including floating drug delivery system. High density DDS, bioadhesive systems, swelling and expanding DDS, modified shape systems and other delayed gastric devices[5,6]. FDDS is suitable for drugs with an absorption window in the stomach or the upper small intestine, for drugs which act locally in the stomach and for drugs that are poorly soluble or unstable in the intestinal fluid DDS or hydro dynamically balanced systems have a bulk density lower than gastric fluid and thus remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. Based on the mechanism of buoyancy, two distinctly different technologies, *i.e.* non-effervescent and effervescent systems, have been used in the development of FDDS[6,7,8]. The effervescent system uses matrices prepared with swellable polymers and effervescent components *e.g.* sodium bicarbonate and citric acid or stearic acid. In non-effervescent FDDS, the drug mixes with a gel forming hydrocolloid, which swells in contact with gastric fluid after oral administration to maintain a relatively stable shape and a bulk density of less than unity within the outer gelatinous barrier[9].

MATERIAL AND METHOD

Material

Preformulation Study of Drug

Preformulation testing is the first step in the rational development of dosage forms of a drug. It can be defined as an investigation of physical and chemical properties of drug substance, alone and when combined with excipients. The overall objective of preformulation testing is to generate information useful to the formulator in developing stable and bioavailable dosage forms, which can be mass-produced[10,11].

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Table 1: Formulation Chart of Floating-Mucoadhesive Tablet of Clopidogrel.

Ingredients	Formulation code								
Quantity (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Clopidogrel	75	75	75	75	75	75	75	75	75
HPMC K4M	50	50	50	60	60	60	70	70	70
Carbopol 934	10	15	20	10	15	20	10	15	20
Sodium Bicarbonate	30	30	30	30	30	30	30	30	30
Citric acid	10	10	10	10	10	10	10	10	10
Mg Stearate	3	3	3	3	3	3	3	3	3
Lactose	47	42	37	37	32	27	27	22	17
Total Weight	225	225	225	225	225	225	225	225	225

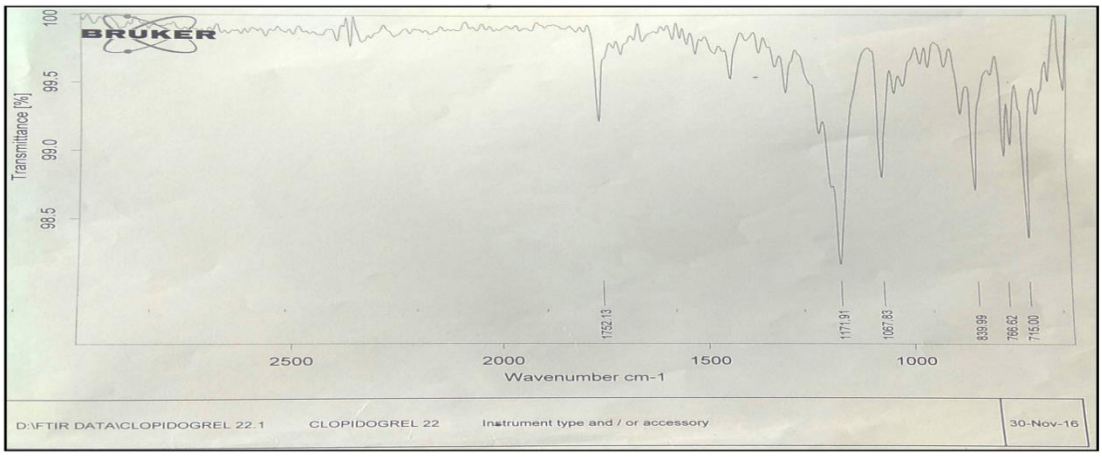

Figure 1: FTIR Spectrum of Clopidogrel.

Table 2: Pre-Compressed Evaluations.

Formulation code	Bulk density (gm/ml)	Tapped density (gm/ml)	Angle of Repose (θ)	Compressibility index (%)	Hausner's ratio
F1	0.352±0.0040	0.416±0.0043	29.27±0.63	15.27±0.11	1.18±0.015
F2	0.365±0.0035	0.425±0.0042	28.62±0.57	14.01±0.10	1.16±0.005
F3	0.374±0.0032	0.412±0.0098	28.63±0.50	9.23±0.69	1.10±0.008
F4	0.387±0.0037	0.435±0.0026	26.57±0.56	11.02±0.55	1.12±0.006
F5	0.383±0.0032	0.442±0.0026	27.82±0.61	13.38±0.72	1.15±0.009
F6	0.361±0.0015	0.410±0.0025	27.64±0.54	12.03±0.24	1.13±0.003
F7	0.380±0.0036	0.459±0.0064	27.29±0.37	17.13±0.46	1.20±0.006
F8	0.376±0.0035	0.442±0.0060	29.35±0.52	14.80±0.16	1.17±0.024
F9	0.379±0.0021	0.441±0.0049	29.53±0.42	13.91±0.13	1.16±0.018

Table 3: Post-Compressed Evaluations.

Formulation code	Hardness (kg/cm^2) ± S.D.	Drug content (%) ± S.D.	(%) Friability ± S.D.	Swelling index %	Thickness (mm)	Weight Variation (mg)
F1	3.42±0.058	88.35±0.040	0.166±0.033	34.07±0.67	3.76 ±0.26	224.13± 1.7
F2	3.51±0.074	89.00±0.027	0.219±0.047	40.73±0.74	3.87±0.15	223.81±0.01
F3	3.54±0.077	98.42±0.018	0.296±0.081	51.55±0.89	3.98±0.21	224.07±0.01
F4	3.32±0.055	91.69±0.029	0.341±0.181	42.22±0.89	3.91±0.41	224.3±0.023
F5	3.53±0.050	90.61±0.010	0.368±0.041	43.70±0.67	3.99±0.68	225.19±1.69
F6	3.58±0.079	95.53±0.017	0.372±0.028	44.88±0.44	3.90±0.12	225.12±0.16
F7	3.56±0.085	93.22±0.023	0.511±0.026	46.07±0.67	3.90±0.49	224.8±0.018
F8	3.57±0.05	92.65±0.030	0.534±0.33	47.25±2.10	3.91±0.16	224 ± 0.018
F9	3.77±0.011	95.14±0.025	0.610±0.23	47.40±0.68	3.93±0.08	225.35±0.15

Identification Tests

Organoleptic Properties

The sample of Clopidogrel was studied for organoleptic characteristics such as colour, odour and appearance[10,11].

Melting Point

Table 4: Floating duration time and Floating lag time.

Formulation code	F1	F2	F3	F4	F5	F6	F7	F8	F9
Floating time (hr.)	12	12	12	12	12	12	12	12	12
Floating lag time (sec)	60	65	77	100	129	148	165	216	230

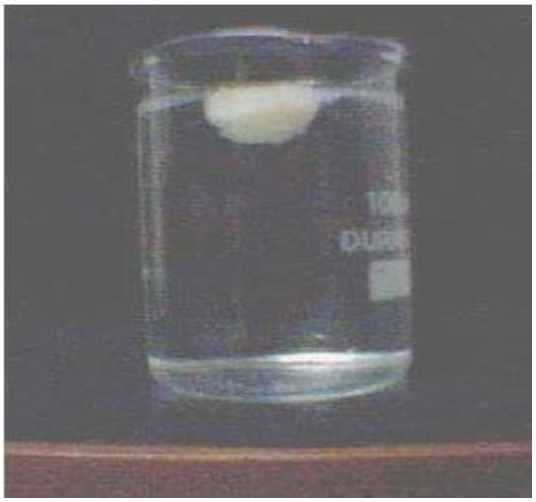

Figure 2: Floating tablet Formulation.

Mucoadhesive Strength

Table 5: Mucoadhesive Strength and Force of tablet

Formulation code	Mucoadhesive Strength (gm)	Mucoadhesive force (dyne)
F1	10.15 ± 0.56	0.5657
F2	11.03 ± 0.02	0.6147
F3	20.05 ± 0.01	1. 1175
F4	12.50 ± 0.02	0.6967
F5	16.21 ± 0.07	0. 9035
F6	13.18 ± 0.01	0. 7346
F7	18.17 ± 0.05	1. 0127
F8	17.17 ± 0.01	0.9569
F9	16.85 ± 0.01	0.9391

Melting point of Clopidogrel was determined by taking a small amount of sample in a capillary tube closed at one end and placed in melting point apparatus. The melting point was noted in triplicate and average value was noted[10,11].

IR Spectroscopy

The FT-IR spectrum of the obtained sample of drug was compared with the standard FT-IR spectra of the pure drug.

Solubility analysis

Preformulation solubility analysis was done to select a suitable solvent system to dissolve the drug and also to test its solubility in the dissolution medium which was to be used.

Differential Scanning Calorimetry

The powdered sample (3 mg) was hermetically sealed in aluminium pans and heated at a constant rate 10^0C/min, over a temperature range of 30-300^{0}C with nitrogen flow rate of 30ml/min. Thermograms of the samples were obtained using differential scanning Calorimetry (DSC-60, Shimadzu, Japan). Thermal analysis data were recorded with Shimadzu software programs. Indian standard was to calibrate the DSC temperature and enthalpy scale.

Compatibility studies

IR Spectroscopy

Compatibility study was carried out by using Fourier Transform Infrared Spectrophotometer (BRUCKER). IR study was carried on pure drug. Physical mixture of drug and excipients were prepared and samples kept for 1 month at 40^{0}C. The infrared absorption spectrum of Clopidogrel and physical mixture of drug and excipient was recorded using diamond disc[12,13].

Preparation of o.1 N HCL

8.5 ml of concentrated HCL was taken and diluted with distilled water up to 1000 ml.

Preparation of Standard Calibration curve of Clopidogrel

The UV spectrum of Clopidogrel was obtained by using UV (Shimadzu UV - 1800, Japan). Accurately weighed 10 mg of the drug was dissolved in sufficient quantity of 0.1 N HCl and volume made up to 10 ml. The stock solution was diluted to obtain a concentration of 100 µg/ml. 1 ml of aliquot was withdrawn and volume was made up to 10 ml using 0.1 N HCl to obtain the concentration of 10 µg/ml. The resultant solution was scanned from 400 to 200 nm and the spectrum was recorded to obtain the value of maximum Wavelength in respective solvents[10,11].

Formulation and Preparation of Floating-Mucoadhesive Clopidogrel tablet by direct compression

Weight all the ingredient accurately fist add polymer HPMC K4M in mortar then Carbopol 934 & Sodium bicarbonate mix it well for 10 min then add drug , magnesium stearate & lactose blend for 10 min at the last magnesium stearate 1% add mix all ingredient homogenously to form a tablet mix for direct compression[14].

Evaluation of powder

The flow properties of granules (before compression) were characterized in terms of angle of repose, tapped density, bulk density, Carr's index and Hausner's ratio[3,4,15].

Determination of Swelling Index

The swelling properties of matrices containing drug were determined by placing tablet matrices in the dissolution test apparatus in 900 ml 0.1 N HCl at 37 ± 0.5^{0}C. The tablets were removed periodically from the dissolution medium and, after removing free water, the weight gain was measured. The swelling characteristics were expressed in terms of the percentage water uptake (WU %) according to the equation[5].

Determination of Floating capacity

Three individual tablets from each formulation were put in an individual flask containing 400ml of 0.1 N HCl solutions. Then note time in minutes for each tablets to go from the bottom to the top of the flask (floating lag time) and the time for which tablets constantly float on the water surface (duration of floating) were measured. The sample mean and standard deviation were calculated.

In-vitro Disintegration Time

Disintegration time was determined using USP

In-Vitro release study

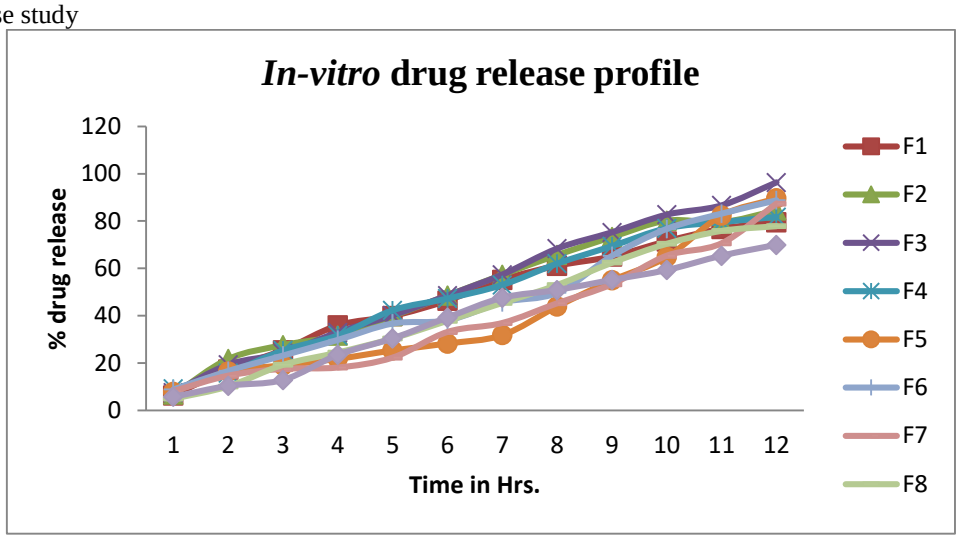

Figure 3: Dissolution Profile of Formulation Batches (F1-F9) (Time Vs %CDR)

A) Surface Response Plots:

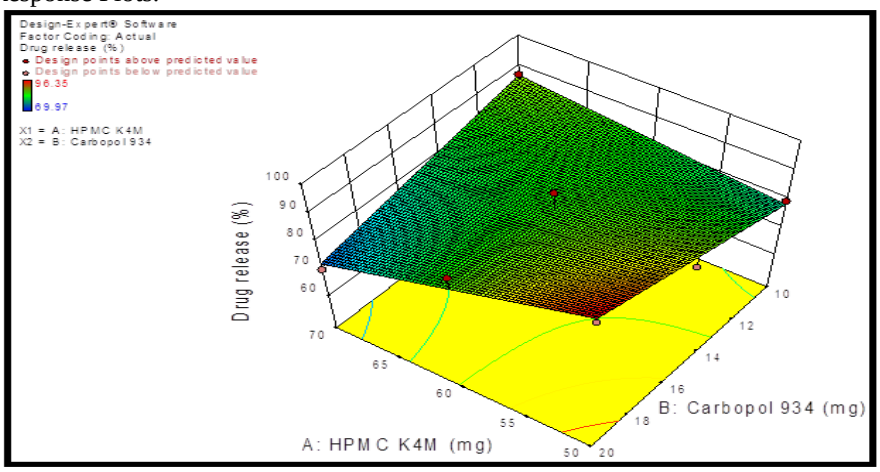

Figure 4: Surface Response plot showing effect of Carbopol 934 and HPMC K4M on drug release

B) Contour plot:

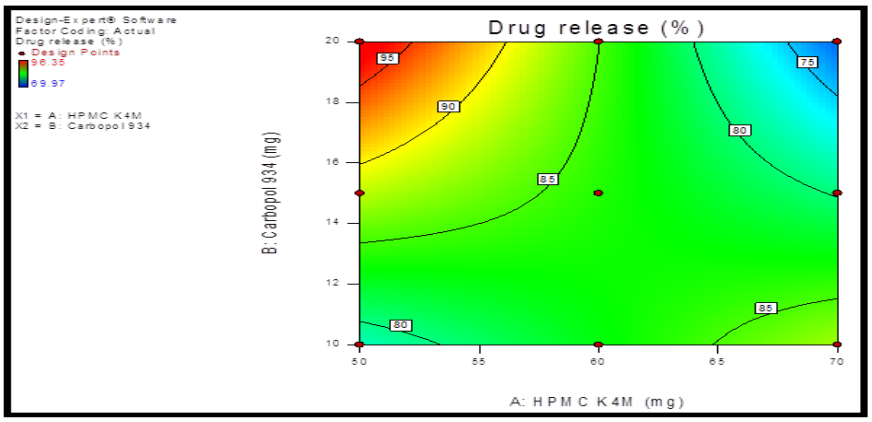

Figure 5: Contour plot showing effect of Carbopol 934 and HPMC K4M on drug release.

disintegration apparatus with distilled water. The volume of medium was 900 ml and temperature was 37 ± 0.2^{0}C. The time in minutes taken for complete disintegration of the tablet with no palatable mass remaining in the apparatus was measured. To comply the test all tablets should disintegrate within 15 minutes.

Drug Content

Units were selected at random and drug content was determined as specified in monograph. The tablet

Zero-order comparative evaluation model kinetics:

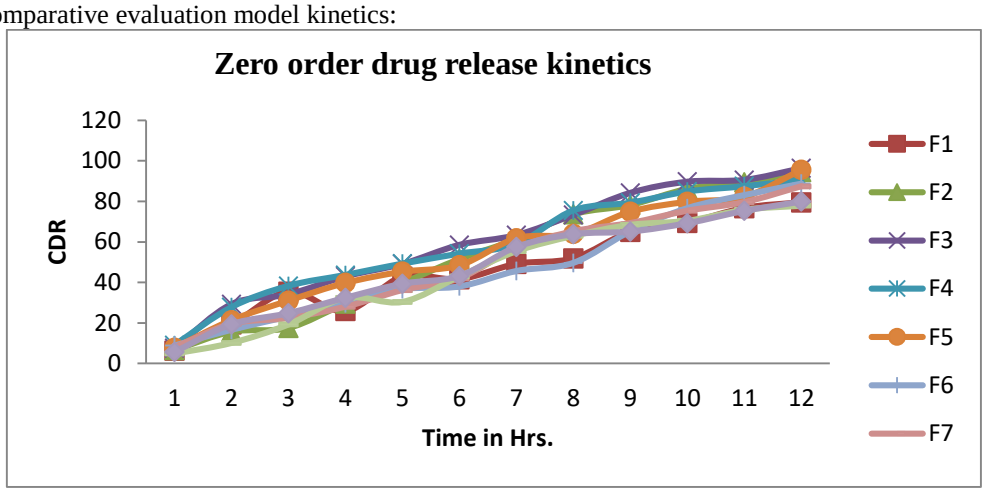

Figure 6: Model graph for comparative evaluation of zero order release kinetics

First-order comparative evaluation model kinetics:

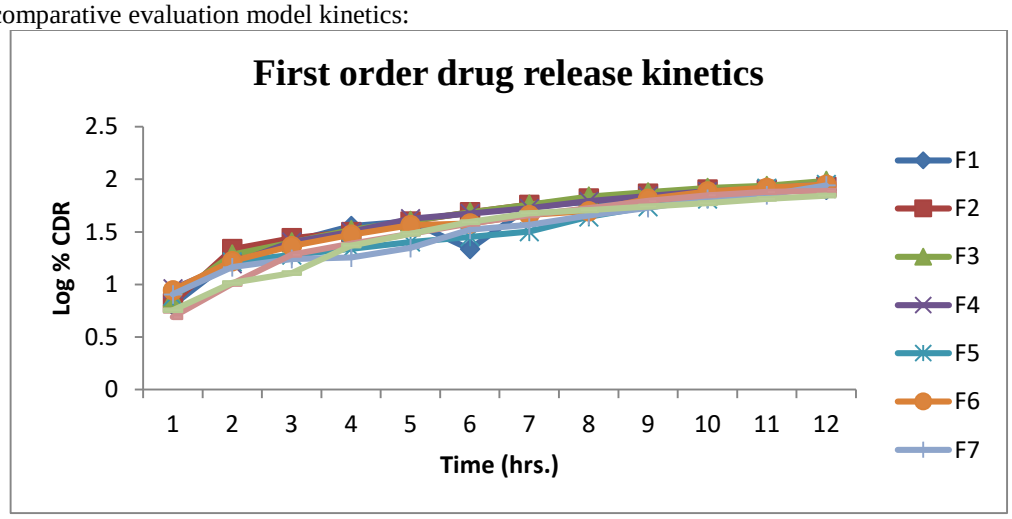

Figure 7: Model graph for comparative evaluation of First order release kinetics

Higuchi and Connor's model release kinetics:

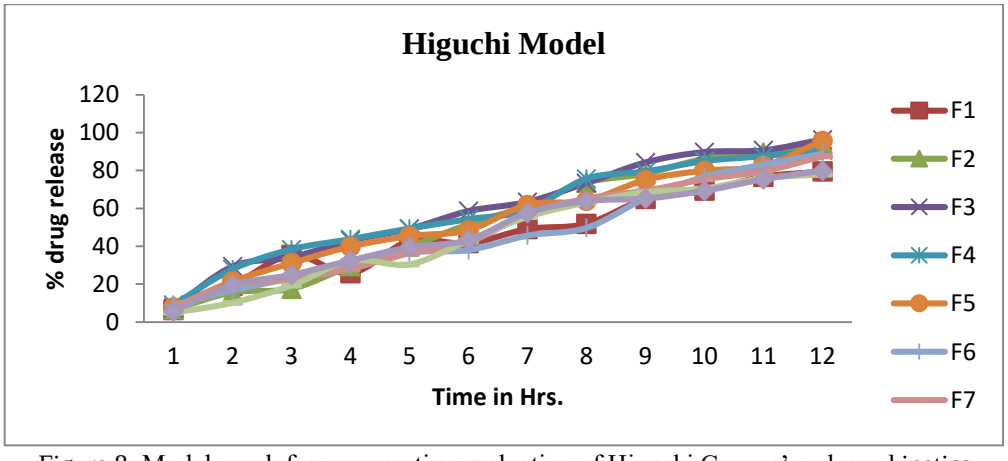

Figure 8: Model graph for comparative evaluation of Higuchi Connor's release kinetics

preparation complies with the test, only if each individual content lies between 85 to 115% of the average content[4].

In vitro mucoadhesion studies

The mucoadhesive strength of the tablets was measured on modified physical balance. The apparatus consist of a modified double beam physical balance in which the right and left pan were with lighter pans. The left side of the balance was made heavier than the right side by placing a 5 g weight on left side pan. Another Teflon block of 3.8 cm diameter and 2 cm height was fabricated with an upward protrusion of 2 cm height and 1.5 cm diameter on

Korsemeyer's peppas comparative evaluation model kinetics

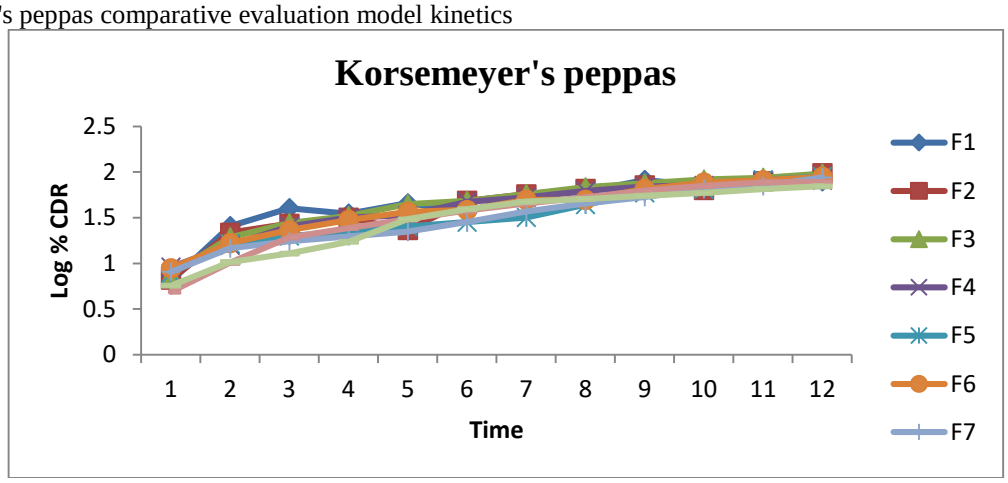

Figure 9: Model graph for comparative evaluation of Korsemeyer's peppas release kinetics

Table 6: Stability study for optimized formulation F3 at 40±2ºC+75% RH.

Formulaton code	1 month	2 month	3 month
F3	98.42 % ± 0.018	97.98 % ± 0.060	97.50 % ± 0.032

one side. This was kept in the beaker, which was then placed below the left hand set of the balance.

The goat gastric mucus membrane was used as the model membrane and pH 1.2 buffer solution was used as the moistening fluid. The goat stomach mucosa was kept in tyrode solution at 37oC for 2 hr. The underlying mucus membrane was separated and washed thoroughly with a pH 1.2 buffer solution. It was then tied to a Teflon-coated glass slide and this slide was fixed over the protrusion in the Teflon block using a thread. The block was then kept in a beaker containing pH 1.2 buffer solution at a level that just touches the membrane so as to moisten the membrane. By keeping a 5 g weight on the right pan that two sides were balanced. The beaker with the Teflon block was kept below the left hand setup of the balance. The tablet was stuck on to the lower side of the left hand side pan. The 5 g weight from the right pan was then removed. This lowered the left pan along with the tablet over the membrane with the weight of 5 g. This was kept undisturbed for 3 min. Total weight minus 5 g was taken as the measure of the mucoadhesive strength from the mucoadhesive strength, the force of adhesion was calculated using following formula;

Force of adhesion (N) = Mucoadhesive strength/100 × 9.81.

In Vitro drug release kinetics studies

Kinetic model had described drug dissolution from solid dosage form where the dissolved amount of drug is a function of test time. In order to study the exact mechanism of drug release from the tablets, drug release data was analyzed according to zero orders, first order, Higuchi square root, korsmeyer peppas model.

RESULT AND DISCUSS

Compatibility study by IR spectroscopy

The FTIR spectra of pure Clopidogrel showed the peaks at wave numbers (cm^{-1}) which correspond to the functional groups present in the structure of the drug.

Evaluation of Formulation

The Clopidogrel tablets were prepared by direct compression method. Ingredients were accurately weighed and passed through mesh. The powder blend was studied for rheological characteristics. The uniformly blend of powder was then compressed in a 10 station tablet punching machine using 12 mm flat faced punches[16].

Before compression powder bed of all formulations were studied for various rheological characteristics bulk density, true density, compressibility index, Hausner's ratio. The results of the studies indicated that the powder bed is easily compressible, and hence can be compressed into a compact mass of tablets. The angle of repose is an indicative parameter of powder Flowability from hopper to die cavity[17].

A repose angle between 25^0 to 30^0 indicates excellent Flowability of powder bed. In this work, the angle of repose was found to be varying between 22.81^0 and 26.72^0 when glidants were incorporated. These studies indicated that, the powder beds of all formulations are easily flowable.

Evaluation of Pre-compressed parameters

All formulations were studied for various rheological characteristics bulk density, true density, compressibility index, Hausner's ratio and angle of repose. The results of the studies indicated that the powder is blend is easily compressible.

Evaluation of Post Compressed Characteristics

The results of Hardness, Disintegration time, Drug content, Friability, Swelling index, Floating time all are summarized in the table given below:

Appearance

The developed formulation met all the pre-requisite to become a floating mucoadhesive tablet, swelled and floated instantaneously at the acidic condition of the stomach.

Drug release kinetics

In the present study, the drug release was analysed to study the kinetic of drug release mechanism. The results showed that the factorial design batches followed zero order and first order model kinetics, Higuchi and Connor's model kinetics and kosemeyer's peppas model kinetics[20,21,22].

Stability Studies

The selected formulation were wrapped in aluminium foil and stored at 40 ± 2ºC and % RH 75% ± 5% temperature for 3 months. After 3 months the formulation F3were evaluated for the hardness, drug content and *in-vitro* % drug release. It was observed that there was no significant variation in the physical appearance, average weight, hardness and loss of drying after placing the tablets at various temperature and humidity conditions for a period of 3 months. Also the cumulative % drug release data showed that each of the formulation released a drug amount, within the limits laid down as per the ICH guidelines for stability studies[23,24,25].

CONCLUSION

The present study was carried out to develop the floating mucoadhesive drug delivery of Clopidogrel using HPMC K4M and Carbopol 934 polymers as the carrier. Clopidogrel is BCS class II drug having low solubility and high permeability. Its oral bioavailability is less than 50% and biological half-life is also approximately 7-8 hrs. All the above reason are suitable for gastro retentive drug delivery system. After procurement of drug sample it was characterized for identification by FTIR. After identification check compatibility of drug with all excipient. It was found that it is compatible with all excipient there is no change in functional group. Physical property of Clopidogrel tablet i.e. hardness, friability, average weight, thickness also complies with standard reference. Floating lag time of all nine formulation show within one minute total floating time was more than 12 hrs. The *In-vitro* drug release profile indicated that batch (F3) was most promising formulation as the extent of drug release from this formulation was high as compare to other formulations, which are suitable for sustained release drug delivery system. The batch F3 shows 96.35% release in 12 hrs, so we concluded that rate of drug release increases in acidic environment of stomach. Release kinetic data of all the formulation show that F1-F9 formulation follows Korsmeyer-Peppas model. Stability study was conducted on tablets of batch F3 at 40±2^{0}C for 3 months. Tablets were evaluated for drug release pattern, hardness, floating behavior and *In-vitro* mucoadhesion. From the discussion it was concluded that the tablets of batch F3 had considerable mucoadhesion along with considerable floating and swelling behaviors with good drug release pattern. Tablets of batch F3 was selected as optimum batch and evaluated for stability study.

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