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Formulation, Evaluation and Optimization of Bilayer Floating Tablet of Repaglinide and Glipizide

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ABSTRACT

The aim of the present research was to develop a bilayer floating drug delivery system. That contains two layers immediate release layer and sustain release layer. First immediate release layer quickly releases drugs and attains onset of action, subsequently floating sustained release layer floats over gastric fluid and releases the drug in sustained or controlled manner. In bilayer tablet formulation, the floating sustained release layer was compressed and immediate release layer was added over it, then both layers were compressed. Tablets were characterized using the official methods. Immediate release layer contained Repaglinide, Sodium starch glycolate & Microcrystalline cellulose. In this study floating sustain release layer tablets were prepared using HPMC K4M alone, Na CMC alone & combination of HPMC K4M & Na CMC. Sodium bicarbonate & Citric acid were used as an effervescent agent. All formulations were prepared by using factorial design (3^2 & 2^3). All the above formulations were evaluated for *in vitro* drug release, buoyancy lag time (BLT), swelling ability, floating behavior. All formulations showed anomalous transport mechanism. This means diffusion as well as swelling controlled had played an essential role in drug release. Finally bilayer floating sustained release tablets was formulated by using optimized immediate release layer and optimized floating sustained release layer & evaluated as earlier. The optimized bilayer tablet formulation was subjected to stability study 40°C±2°C/75%RH±5%RH for 1 month according to ICH guidelines & evaluated. From the study it is concluded that the developed formulation has good appearance with good handling condition, therapeutically efficacious, stable. The developed Bilayer formulation is viable alternative to conventional Repaglinide and Glipizide tablet.

KEYWORDS

Bilayer floating tablet, buoyancy lag time, Factorial design, HPMC K4M and Na CMC.

INTRODUCTION

Bilayer tablets contain immediate and sustained release layers. The immediate release layer delivers the initial dose, it contains superdisintegrants which promotes drug release rate and attains the onset of action quickly whereas sustained release layer float due to gas generating agents and releases drug at sustained manner for prolonged time period.

The biphasic system is used mostly when maximum relief needs to be achieved quickly and it is followed by a sustained release phase.

It also avoids repeated administration of drug. Coronary vasodilators, antihypertensives, antihistaminics, analgesics, antipyretics and antiallergenic agents are mainly suitable for this system.

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The biphasic system some time may contain two drugs in separate release layers.

Bilayer tablet approach

- One is immediate release and other is sustained release layer.
- Two drugs in same tablet with different layers.
- Tablet having sustained release layer and floating layer.

Gastric emptying is a complex process, which is highly variable and make the drug delivery systems uncertain. In order to avoid this variability, efforts have been made to increase the retention time of the drug delivery systems for more than 12 hrs. The floating or hydrodynamically controlled drug delivery systems are useful in such applications. However, many floating systems previously reported are single-unit systems such as HBS, which are unreliable in prolonging the GRT owing to their 'all-or-nothing' emptying process and, thus, may result in high variability in bioavailability and local irritation due to a large amount of drug delivered at a particular site of GIT.

The conventional dosage forms retained in the stomach for 0.5-2 hrs and passes to small intestine and where it gets absorbed within 3-6 hrs. Therefore it is difficult to adjust release retardation and stomach retention of drug for longer period of time. The concept of gastroretentive drug delivery system came from the need to localize the drug at a certain site in the body. In oral drug delivery, drug absorption is limited due to the gastrointestinal transit time of the dosage form. When the site of drug absorption is mainly stomach or upper part of GIT, then it is necessary to retain the dosage form at the site of absorption for longer duration, but the gastrointestinal transit is the limitation for such type of dosage forms. Therefore gastroretentive dosage forms are formulated to increase the gastric residence time. The majority of drugs are preferentially absorbed from the upper part of GIT hence, drug release at site of absorption can improve therapeutic efficacy of drug.

Drugs having pH dependent solubility i.e. highly soluble at low pH (gastric pH) and poorly soluble at high pH (intestinal pH), drugs having short biological half life e.g. Glipizide are the suitable drug candidates for the formulation of floating sustained drug delivery system.

Glipizide second generation sulfonylurea an oral hypoglycemic agent, is one of the most commonly prescribed drugs for the treatment of patients with type II diabetes mellitus, its half life 2-4 hrs the gastroretentive drug delivery systems can be able to retain the dosage unit in the stomach and assist in improvement of solubility of drugs. Therefore, Glipizide is a suitable model drug candidate for gastroretentive formulation.

MATERIAL AND METHOD

Material

Repaglinide and Glipizide received as a gift sample from Bharat Perenterals Limited. Sodium Carboxymethyl Cellulose and Hydroxypropyl Methylcellulose K4M were procured from Vasu Pharmachem. Citric acid, Magnesium Stearate, Microcrystalline Cellulose, Sodium Laury Sulphate, Sodium Starch Glycolate, Sodium Bicarbonate, Polyvinyl Pyrolidone were procured from local market.

Formulation of Bilayer Floating Tablets

Bilayer tablet contains two layers i.e. immediate release layer of Repaglinide and sustained release layer of Glipizide. Bilayer tablets were prepared by using optimized immediate and sustained release layer. Accurately weighted 50 mg of immediate release layer and 100 mg of floating sustained release layer individually. Various batches of bilayer tablets were prepared by direct compression method according to Table 1. Initially immediate release powder blend was fed manually into the die of 10 stations Cadmach CMD 3-16 tablet machine and then compressed at low compression force to form uniform layer. Subsequently floating sustained release layer powder blend was added over that layer and completely compressed on rotary tablet punching machine by using flat faced punch 7 mm.

Table 1: Compositions of Bilayer Floating Tablet (150 mg)

Ingredients (mg)	Formulation Code					
	AA5	AA6	AA9	AC2	AC3	AC4
Immediate release layer(50 mg)						
Repaglinide	2	2	2	2	2	2
Sodium Starch Glycolate	04	04	04	04	04	04
Avicel MCC 102	43	43	43	43	43	43
Sodium lauryl sulphate	1	1	1	1	1	1
Floating Sustained layer(100 mg)						
Glipizide	10	10	10	10	10	10
Sodium Bicarbonate	20	20	20	10	10	10
Citric Acid	04	04	04	04	04	04
HPMC K4M	30	20	10	10	20	10
Na CMC	….	….	….	10	10	20
PVP K30	10	10	10	10	10	10
Sodium lauryl sulphate	01	01	01	01	01	01
Magnesium stearate	01	01	01	01	01	01
Avicel MCC 102	24	34	44	44	34	34

*HPMC – Hydroxypropyl methylcellulose, MCC-Microcrystalline cellulose.

Steps Involved in Bilayer Floating Tablet Preparation

1. Filling immediate release powder blend into dies.
2. Slightly compressed immediate release powder blend.
3. Ejection of upper punch.
4. Addition of floating sustained release powder over immediate release powder.
5. Compression of both layers.
6. Ejection of bilayer tablet.

Evaluation of Post-Compression Parameters for Floating Sustained Release Tablets

Prepared floating sustained release tablets were evaluated for post-compression parameters such as hardness, thickness, friability, weight variation, floating behaviour (BLT & TFT), swelling study, drug content, *in vitro* drug release study, kinetics of *in vitro* drug release.

Determination of Buoyancy Lag Time (BLT) & Total Floating Time (TFT)

Buoyancy lag time is the time required for the tablet to rise towards surface and float. The buoyancy of tablets was studied at 37 ± 0.5 ºC in 200 ml of 1.2 pH buffer. (8.5 ml of concentrated Hydrochloric acid was taken and added to 1000 ml of water and measured the pH of solution) The buoyancy lag time was measured by using stop watch and total floating time was observed visually.

***In vitro* Drug Release Study[19]**

In vitro drug release study was performed using type-II (paddle) apparatus at 50 rpm in 900 ml simulated gastric fluid of 1.2 pH for 12 hrs. Temperature was maintained at 37 ± 0.5ºC. The 5 ml sample was withdrawn at predetermined time intervals and replaced with same fresh dissolution media. The withdrawn samples were filtered through membrane filter 0.45µm and analyzed by using UV spectrophotometer at λ_{max} 241 nm and λ_{max} 276nm for 1hr and then after

λ_{max} 276 for 12 hrs. This test was performed on 3 tablets and mean ± SD was calculated.

Kinetics of *In-vitro* Drug Release

To study the release kinetics of *in vitro* drug release data of above selected batches were applied to kinetic models such as zero order, first order, Higuchi and Korsmeyer- Peppas.

Zero order

$C=K_0t$…… (1)

Where, K_0 is the zero-order rate constant expressed in units of concentration/time and t is the time in hrs.

First order

$dC/dt=KCo$…..……(2)

Where, C_0 is the initial concentration of drug, K is the first order constant, and t is the time in hrs.

The drug diffusion through most types of polymeric systems is often best described by Fickian diffusion, but other processes in addition to diffusion are important. There is also a relaxation of the polymer chains, which influences the drug release mechanism. This process is described as non-Fickian or anomalous diffusion. Release from initially dry, hydrophilic glassy polymers that swell when added to water and become rubbery show anomalous diffusion as a result of the rearrangement of macromolecular chains. The thermodynamic state of the polymer and the penetrant concentration are responsible for the different types of the diffusion. This is a special case of non-Fickian diffusion. A simple, semiempirical equation can be used to analyze data of controlled release of water-soluble drugs from polymer matrices (Eq.3). This equation predicts the mechanism of diffusion release.

$Mt/M\infty=Kt^n$…… (3)

Where, Mt is amount of the released drug at time t, $M\infty$ is the overall amount of the drug (whole dose), K is the constant incorporating structural and geometric characteristics of the controlled release device, and n is the release exponent indicative of the drug release mechanism.

If the exponent n = 0.5, then the drug release mechanism is Fickian diffusion. If n < 0.5 the mechanism is quasi-Fickian diffusion, and 0.5 < n < 1.0, then it is non-Fickian or anomalous diffusion and when n = 1.0 mechanism is non Fickian case II diffusion, n> 1.0 mechanism is non Fickian super case II. In this study the number n was calculated for the time interval from the 1 to 12 h, because in the first hrs the burst effect was recognised (the drug releases from the surface of the tablet, before gel layer formation). The result for all formulation revealed that the calculated n is characteristic for the non-Fickian type of drug diffusion, which means that the processes of diffusion and relaxation run at comparable rates**.**

The passage of a water-soluble drug through hydrated gel layer around the matrix tablet is approximately dependent on the square root of time and can be described in the following form.

$Qt=Kt^{1/2}$……....(4)

Where Qt is the amount of the released drug in time t, k is the kinetic constant, and t is time. Many times this simple equation (Eq. 4) is useful for the determination of the drug release rate.

Accelerated Stability Study

It is vital for formulation development person to develop a stable product from formulation as well as regulatory point of view. The regulatory agencies around the globe have rhetoric guidelines of product stability studies. Stability study is performed to check physical and chemical integrity of the formulation.

The optimize formulation was selected for stability study. The tablets were placed separately in two identical glass bottles. One was kept at room condition while other was kept at 45°C and 75% relative humidity (RH).

Temperature condition:

1) Room temperature (30-40°C)

2) 45°C temp. + 75% RH.

Time period: 15 and 30 days

Evaluation parameter: Hardness, Disintegration time, Assay and Dissolution profile.

RESULTS

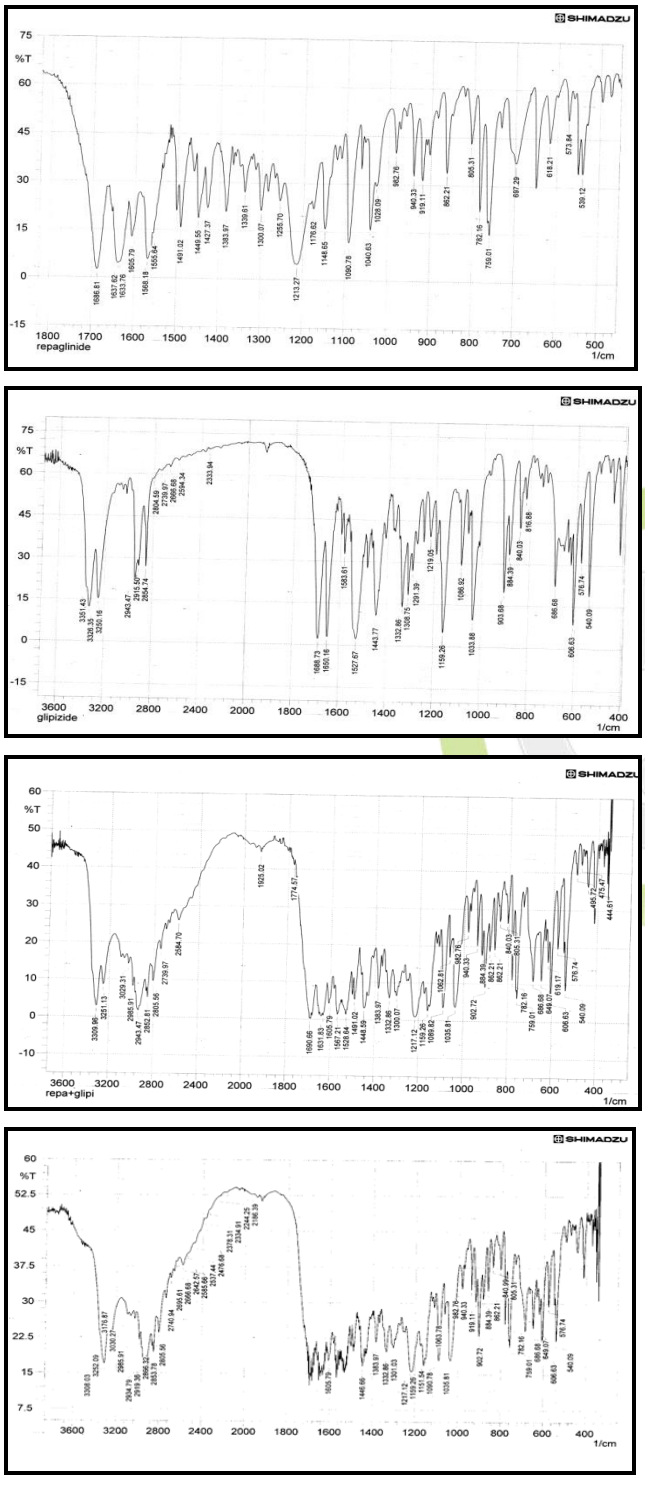

Figure 1: A) Repaglinide B) Glipizide C) Repaglinide with Mixture D) Glipizide with Mixture

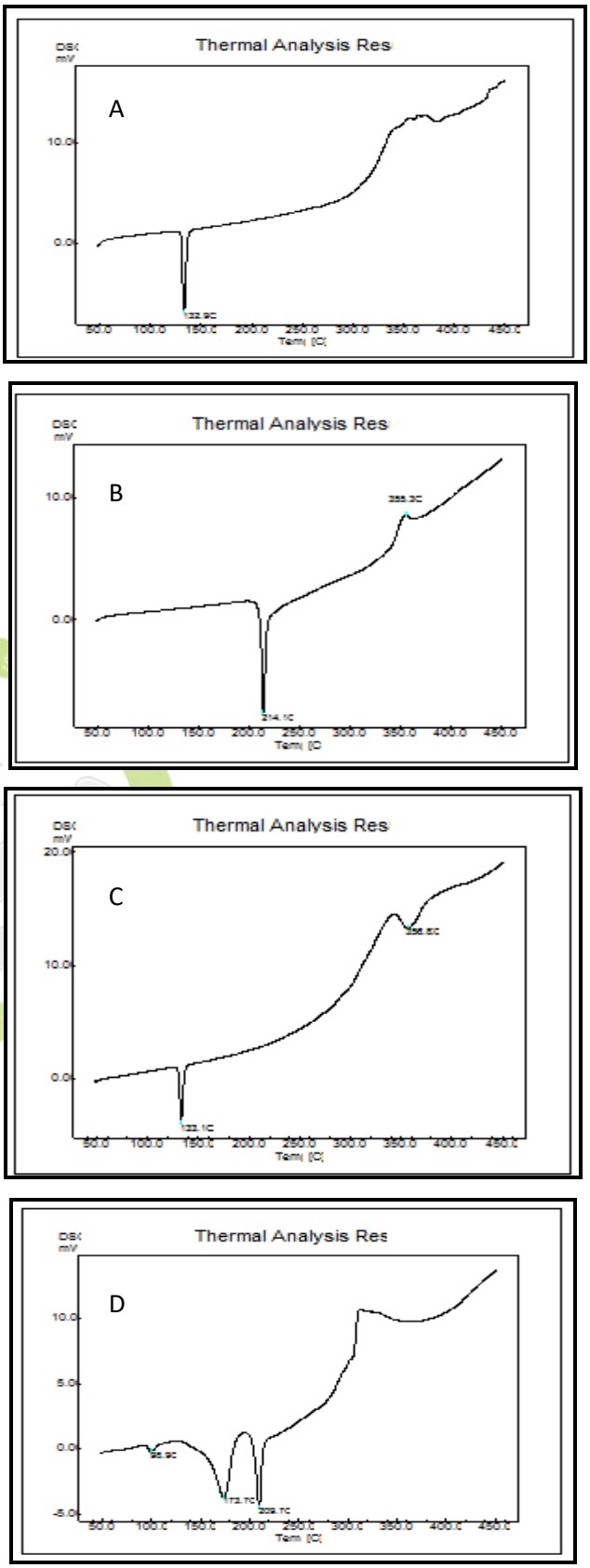

Figure 2: DSC graphs A) Repaglinide B) Glipizide C) Repaglinide with Mixture D) Glipizide with Mixture

Table 2: Evaluation of Pre-compression Parameters of Drugs, Polymers and Excipients

Ingredients	Parameters				
	Angle of Repose (θ)	**Bulk Density gm/cm^3**	**Tapped Bulk Density gm/cm^3**	**Hausner's Ratio (H_R)**	**Compressi-bility Index (%)**
Repaglinide	28.34±1.2	0.27±0.03	0.4±0.02	1.48±0.61	30.5±1.54
Glipizide	29.2±1.7	0.29±0.01	0.37±0.02	1.27±0.34	21.62±1.01
HPMC K4M	33.1±1.4	0.36±0.02	0.42±0.05	1.16±0.24	14.28±0.43
Na CMC	36.52±1.6	0.54±0.05	0.82±0.03	1.51±0.31	34.14±1.63
SLS	33.12±1.5	0.97±0.03	1.54±0.32	1.58±0.46	37.08±1.89
Sodium Bicarbonate	39.54±2.3	0.96±0.35	1.48±0.41	1.54±0.22	35.13±1.04
Citric acid	29.18±1.1	0.61±0.26	0.97±0.43	1.59±0.49	37.11±1.3
SSG	28.82±1.3	0.95±0.04	1.31±0.27	1.37±0.31	27.48±1.1
Mg stearate	34.35±1.56	0.15±0.02	0.28±0.03	1.86±0.54	46.42±1.28
PVP K30	28.43±1.36	0.34±0.04	0.46±0.08	1.35±0.37	26.08±1.05
MCC 102	36.41±1.5	0.26±0.03	0.38±0.06	1.46±0.33	31.57±1.11

Table 3: Evaluation parameter of bilayer floating tablets

Formulation Code	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Weight variation (mg)	Disintegration Time (sec)
AA5	2.68±0.04	6.2±1.3	0.5±0.3	150±2.5	38±1.6
AA6	2.70±0.09	6.0±1.5	0.3±0.1	150±1.4	35±1.8
AA9	2.70±0.08	6.3±1.1	0.4±0.2	149±2.1	37±0.9
AC2	2.72±0.10	6.4±0.9	0.4±0.5	151±1.6	39±1.9
AC3	2.75±0.12	6.0±1.4	0.2±0.1	150±2.3	40±1.3
AC4	2.67±0.07	6.2±1.2	0.3±0.5	149±1.7	38±1.6

Determination of Buoyancy Lag Time

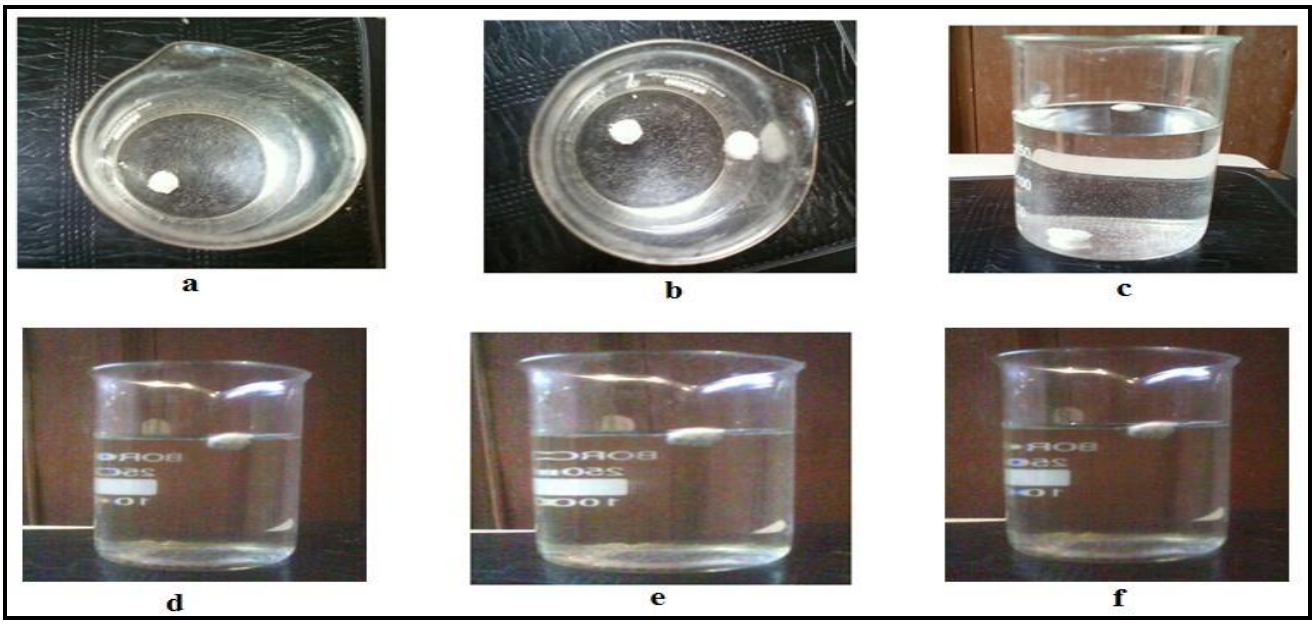

Figure 3: Photograph shows a)- Tablet after 14 Sec, b)- Separation of immediate and sustained release layer from bilayer tablet, c)- Tablet after 5 min., d)- Tablet after 4 hrs, e) - Tablet after 8 hrs, f)- Tablet after 12 hrs (Batch AC2).

Table 4: Evaluation parameter of bilayer floating tablets

Formulation Code	**Floating lag time (sec)**	**Drug content for immediate layer (%)**	**Drug content for sustained floating layer (%)**	***In vitro* drug release for immediate layer**	***In vitro* drug release after 12 hrs for sustained floating layer**	**Total floating time (hrs)**
AA5	125±1.4	95.51±1.3	97.8±1.9	94.47±1.2	89.96±1.4	>12
AA6	138±2.6	96.17±2.1	98.69±1.4	95.93±1.7	92.28±2.7	>12
AA9	145±2.5	97.09±1.5	96.5±1.3	93.92±2.1	88.21±2.9	>12
AC2	142±3.4	97.67±1.8	99.08±1.6	97.33±2.2	95.06±2.2	>12
AC3	135±2.6	98.83±1.1	97.3±1.1	96.75±2.9	93.32±2.9	>12
AC4	137±2.4	99.41±1.2	98.2±1.8	95.59±2.8	90.49±2.8	>12

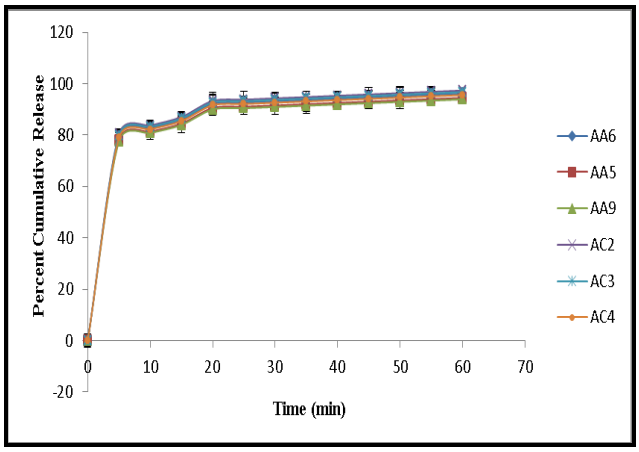

Figure 4: Comparative dissolution study of optimized bilayer floating tablets in 1.2 pH buffer (n = 3, mean ± S.D.) (Immediate release profile)

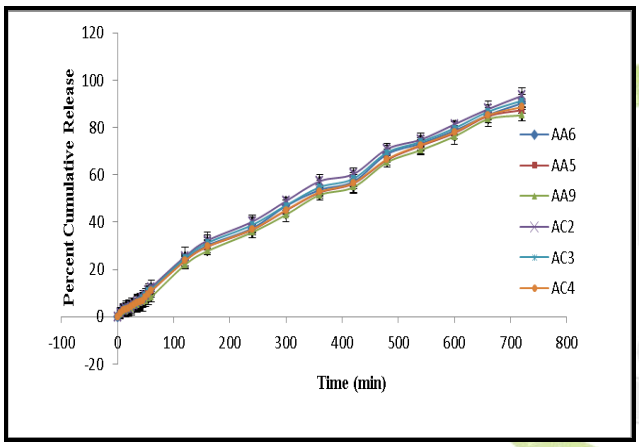

Figure 5: Comparative dissolution study of optimized bilayer floating tablets in 1.2 pH buffer (n = 3, mean ± S.D.) (Floating sustained layer release profile)

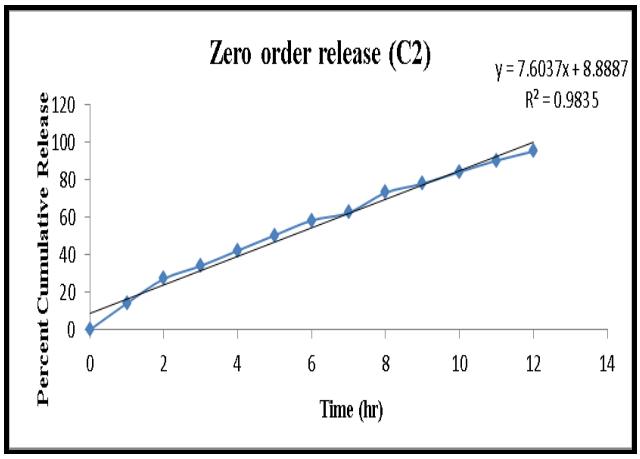

Figure 6: Zero order release (% cumulative release vs. time)

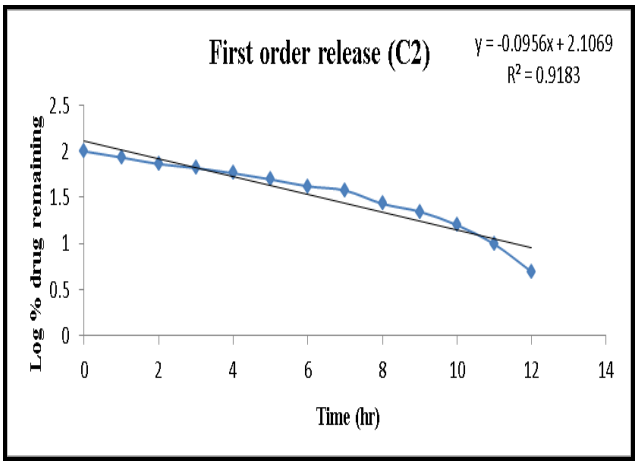

Figure 7: First-order kinetics (log cumulative % drug remaining vs. time)

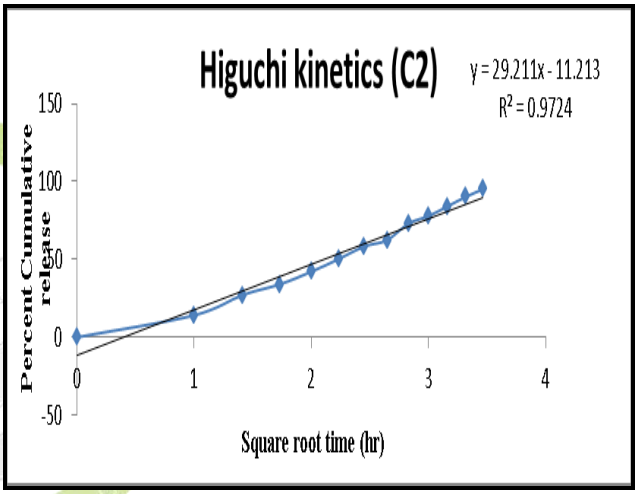

Figure 8: Higuchi kinetics (% cumulative release vs. square root of time)

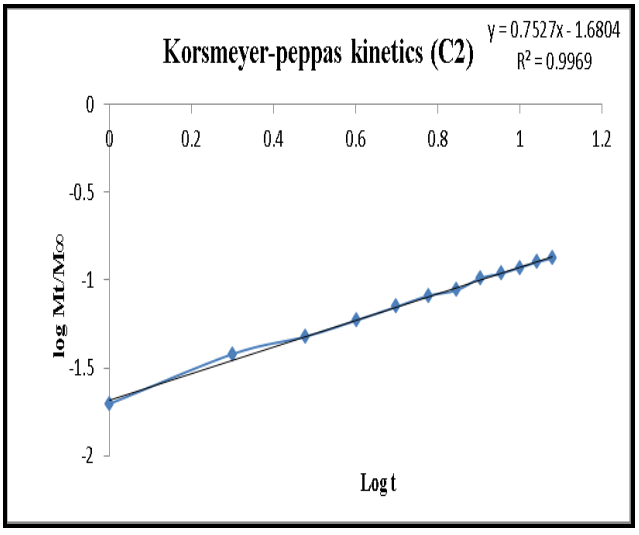

Figure 9: Korsmeyer-Peppas equation (log cumulative % drug released vs. log time)

Table 5: Release Kinetics data of optimized floating sustained release tablet in 1.2 pH buffer.

Formulation Code	**Zero order**	**First order**	**Higuchi**	**Korsmeyer Peppas**	**Korsmeyer Peppas**
	R^2	**R^2**	**R^2**	**R^2**	**n**
AA5	0.987	0.952	0.964	0.995	0.806
AA6	0.985	0.939	0.967	0.995	0.781
AA9	0.990	0.954	0.958	0.991	0.860
AC2	0.983	0.918	0.972	0.996	0.752
AC3	0.985	0.930	0.969	0.996	0.765
AC4	0.991	0.936	0.958	0.997	0.813

Effect of formulation variables on percentage cumulative drug release at 12 hrs

$$\mathbf{Y1 = 94.14 -- 0.56*A -- 1.10*B -- 1.93*C + 0.026*A*B -- 0.17*A*C + 0.32*B*C -- 1.61*A^2 -- 1.26*B^2 – 1.08*C^2} \quad \text{……………………………………………………………(5)}$$

Where, Y1 = % cumulative drug release

A = HPMC K4M
B = Na CMC
C = $NaHCO_3$

Effect of formulation variables on floating lag time

$$\mathbf{Y2 = 45.62 + 0.52*A – 2.57*B – 1.53*C – 1.25*A*B – 1.25*A*C – 1.25*B*C -- 1.82*A^2 – 2.17*B^2 – 1.82*C^2} \quad \text{…………………………………………………(6)}$$

Where, Y2 = Floating Lag Time

A = HPMC K4M
B = Na CMC
C = $NaHCO_3$

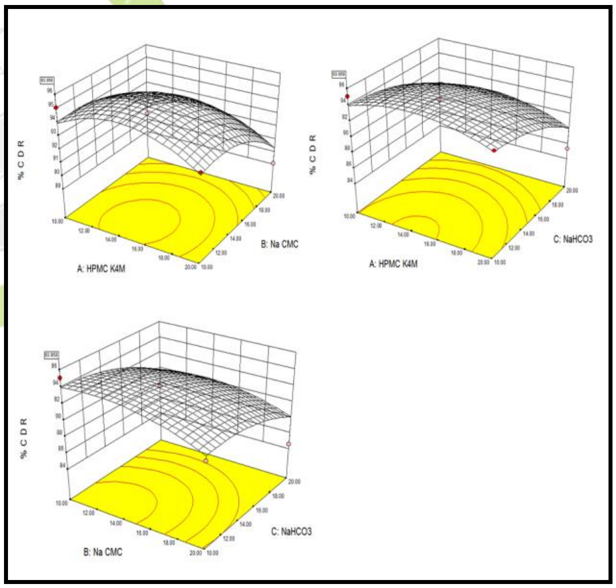

Figure 10: Response surface plots showing the effect of HPMC K4M, Na CMC and $NaHCO_3$ on percent cumulative drug release (*Y*1).

DISCCUSION

The IR spectrum was measured in the solid state as potassium bromide dispersion. The IR spectrum of Repaglinide and Glipizide are presented in figure 1. Repaglinide and Glipizide these peaks are similar to reported peaks of Repaglinide and Glipizide.

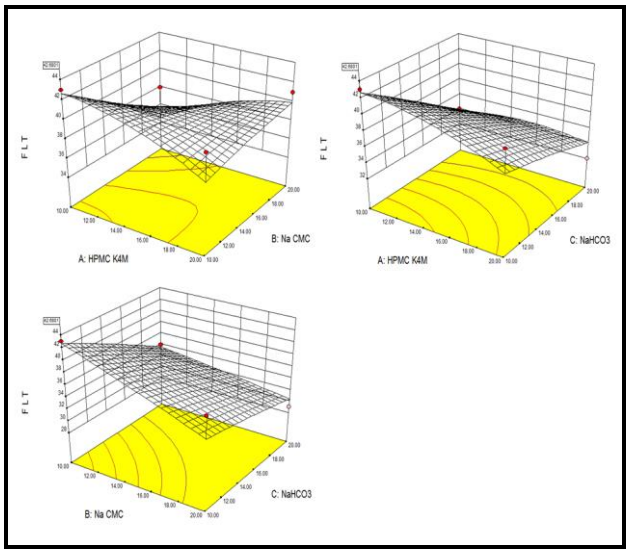

Figure 11: Response surface plots showing the effect of HPMC K4M, Na CMC and $NaHCO_3$ on floating lag time (*Y*2)

Physical mixtures of drug and polymers were characterized by FTIR spectral analysis for any physical as well as chemical alteration of the drug characteristics.

DSC thermogram showed that there was no much more difference in onset temperature and peak temperature, when compared with pure drug's thermogram Figure 2. So no interaction was found between drug and polymers used.

Almost all the batches showed uniform thickness and drug content was in the range of 95-99 % for immediate release layer and 96-99% for sustained release layer. All batches passed weight variation test and found to be within range (150 ± 7.5%) and friability was less than 1%, it indicates that tablet surfaces are strong enough to withstand mechanical shock or attrition during storage, transportation and until they are consumed.

Determination of Buoyancy Lag Time (BLT) was only performed to check the floating behaviour of floating sustained release layer while disintegration test was only performed to check the disintegration of immediate release layer. The buoyancy of bilayer floating tablet was studied at 37 ± 0.5^{o}C in 200 ml of 1.2 pH buffer. The buoyancy lag time (BLT) was measured by using stop watch and total floating time was observed visually**.** Floating lag time was observed less than 150sec for all batches. Total floating time was observed more than 12 hrs.

To study the release kinetics, *in vitro* dissolution data obtained from optimized formulations were applied to various kinetic models viz. zero order, first order, Higuchi release and Korsemeyer-peppas equation.

To confirm the exact mechanism of drug release from these tablets the data were fitted according to the Korsmeyer- Peppas equation. When n takes the value of 0.5, it indicates diffusion controlled drug release and for the value 1.0 it indicates swelling controlled drug release. Values of n between 0.5 and 1.0 can be regarded as an indicator for both phenomena (Anomalous transport).

The value of n in case of all optimized formulation was between 0.5 and 1.0 suggested that the release of Glipizide from the floating tablets followed the anomalous transport mechanism. This means diffusion as well as swelling controlled had an essential role in drug release. Korsmeyer- Peppas plot for batches. All the formulation follow this model.

Regression Coefficients for the Responses Y1 (% cumulative drug release after 12 hrs) is. As the polymers (HPMC K4M and Na CMC) concentration increase an increase in viscosity of the swollen gel matrix, which contribute more hindrance for drug diffusion and consequently decreases the release rate and the relationship between variables was further elucidated using response surface plot shown in figure 10**.** Highest value of percentage cumulative release at 12 hrs was observed in formulation AC2 having low value of the independent variables, which may be due to low polymer concentration.

Regression Coefficients for the Responses Y2 (floating lag time). As the effervescence agent ($NaHCO_3$) and polymers (HPMC K4M and Na CMC) concentration increase an reduce the floating lag time because concentration of polymers (HPMC K4M and Na CMC) increases

the swelling rate and formulation which contained high swelling capacity could lead to greater penetration of the gastric fluid into the tablet leading to faster carbon dioxide gas generation from effervescence agent ($NaHCO_3$), thereby reducing the floating lag-time and the relationship between variables was further elucidated using response surface plot shown in figure 11.

The process was optimized for the response Y1 and Y2, and the optimized formulation (AC2) was arrived at by maximizing the percent cumulative release and the percent cumulative release of optimized formulation was 95.06 % at 12 hrs by experimented work and predicted value for percent cumulative release was 93.95 % and for floating lag time experimented value was 43 sec. and predicted value was 42.68 sec. shown a good relationship between the experimented and predicted values, which confirms the practicability and validity of the model.

No major difference was found between evaluated parameters before and after ageing storage and all were found to be in the acceptable limits.

CONCLUSION

In this study, we successfully developed novel bilayer floating tablet which exhibit a unique combination of floatation for prolonged residence in the stomach by attaining quick onset of action. The optimized tablet formulation AC2, showed satisfactory results in several *in vitro* tests.

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