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DESIGN AND EVALUATION OF BILAYER FLOATING TABLETS OF HYDROXY UREA AND RAMOSETRON

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Abstract:

The purpose of this study to design a bi-layer floating tablets of hydroxy urea (HU) and ramosetron (RS) for delivering multiple pharmaceuticals with atypical release patterns, such as one layer of drug as immediate release (IR) for fast relief and a second layer of drug as sustained release (SR) for long-term effect and reduced dose frequency. The floating layer of HU provides a sustained release by using polymers such as guar gum, carbopal 34 and HPMC K100. The immediate release layer ramosetron developed by using sodium starch glycolate (SSG), crospvidone (CP) as super disintegrants. The tablets are prepared by direct compression method and evaluated for physic chemical parameters such as hardness, thickness, friability, weight variation, in vitro drug release and assay. The optimized formulation (H9) subjected to kinetic release models; the drug release fallows zero order. It can be concluded that the concept of bilayer floating tablets useful for extending the metabolism and improving the bioavailability.

Key words: *Bilayer floating tablet, Susatined release, Hydroxy Urea, and Ramosetron*

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1. INTRODUCTION:

The retention of oral dosage forms in the upper gastrointestinal tract (GIT) causes prolonged contact time of drug with the GI mucosa, leading to higher bioavailability, and hence therapeutic efficacy, reduced time intervals for drug administration, potentially reduced dose size and thus improved patient compliance [(1)]. Therefore, extended release (ER) drug delivery systems possessing gastric retention properties may be potentially useful [(2)].

Bi-layer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances and also for sustained release (SR) tablet in which one layer is immediate release as initial dose and second layer is maintenance dose [(3)]. A Bi-layer tablet has been developed to achieve controlled delivery of different drugs with pre defined release profiles. In the last decade interest in developing a combination of two or more API's in a single dosage form has increased in the pharmaceutical industry, promoting patient convenience and compliance [(4)].

Hydroxyurea (HU) is urea in which one of the hydrogen atoms has been replaced by a hydroxy group. It is an antimetabolite of mono hydroxyl-urea. In addition to treating sickle cell disease, persistent myeloid malignancy is cured with an antineoplastic [(5)]. Ramosetron (RS) is a serotonin 5-HT_3 receptor antagonist that is frequently used to treat nausea, vomiting, and several diarrheal illnesses. It is also proposed for the treatment of irritable digestive ailment in men with diarrhea-predominant signs [(6)].

Hydroxyurea (HU) and Ramosetron (RS) bi layer floating tablets deliver drugs with peculiar release patterns, such as one layer of medicine as instant release (IR) for quick relief and a second as SR for long-term impact and lower dosage frequency.

2. MATERIALS AND METHODS:

2.1. Materials

Hydroxy Urea, and HPMC K100M and ethyl cellulose were from AET Pharmaceuticals, Hyderabad. Ramosetron was given by A.R. Life Sciences Pvt Ltd, Hyderabad. Sodium bicarbonate, Finer chemicals (India) Pvt Ltd. Ahmedabad. PVP K 30 was obtained as gift sample from Dr Reddys Laboratories, Hyderabad. Crospovidone and sodium starch glycolate were procured from Amrutha Organics, Hyderabad. Starch from Karnataka fine chem. Bangalore, magnesium stearate and talc were from S.D fine chem.ltd. All other reagents and chemicals used were of analytical reagent grade.

2.2. Methods

2.2.1. Preparation of floating bilayer tablets

Formulation of bilayer matrix tablet (Floating layer)

The hydroxyurea floating layer was prepared by the direct compression technique with various excipients as per the formula given in Table 1. The drug and additives were passed through sieve 40 and mixed thoroughly in a poly bag for 30 min for uniform mixing. Dried mixture materials were passed through a milling 1.5 mm screen and sifted through sieve 20 and finally lubricated with the magnesium stearate [(7)]. Guar gum, HPMC K 100 and ethyl cellulose act as polymer, sodium bicarbonate act as gas generating agent.

Table 1: Formulation ingredients for floating layer

Ingredients (mg)	H_1	H_2	H_3	H_4	H_5	H_6	H_7	H_8	H_9
Hydroxyurea	200	200	200	200	200	200	200	200	200
$NaHCO_3$	35	35	35	35	35	35	35	35	35
Guar gum	35	52.5	70	-	-	-	-	-	-
Carbopal 34	-	-	-	35	52.5	70	-	-	-
HPMC K100				-	-	-	35	52.5	70
EC	10.5	10.5	10.5	10.5	10.5	10.5	10.5	10.5	10.5
Talc	5.25	5.25	5.25	5.25	5.25	5.25	5.25	5.25	5.25
PVPK30	10.5	10.5	10.5	10.5	10.5	10.5	10.5	10.5	10.5
Magnesium stearate	5.25	5.25	5.25	5.25	5.25	5.25	5.25	5.25	5.25
MCC	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Total weight (mg)	350	350	350	350	350	350	350	350	350

Preparation of immediate release layer of ramosetron:

It was prepared by the direct compression method as per the composition Table 2. Drug (RS), microcrystalline cellulose (MCC) and PVP K30 were passed through sieve 40. All the above were mixed in geometric proportion in a poly bag for 15 min, then required quantity of super disintegrant. Talc and magnesium stearate were passed through sieve 60 and mixed with above blend in a poly bag for 2 min [8].

Table 2: Formulation components of IR layer

Ingredients (mg)	R1	R2	R3	R4	R5	R6	R7	R8	R9
Ramosetron	1	1	1	1	1	1	1	1	1
Talc	3	3	3	3	3	3	3	3	3
SSG	7.5	11.25	15	-	-	-	-	-	-
CP	-	-	-	7.5	11.25	15	-	-	-
CCS	-	-	-	-	-	-	7.5	11.25	15
PVP K30	3.75	3.75	3.75	3.75	3.75	3.75	3.75	3.75	3.75
Magnesium stearate	3.75	3.75	3.75	3.75	3.75	3.75	3.75	3.75	3.75
MCC	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Total weight (mg)	100	100	100	100	100	100	100	100	100

Bilayered tablet punch

After the batch was optimized in both immediate release layer (R1) and sustained release layer (H9).The optimized batch in both was compressed by using same ingredients, given in Table 3.

Table 3: Formulation ingredients for bilayerd tablet

Sustained Release Formula (H9)	Bilayered formulation (F10)
HYDROXYUREA	200
PVPK30	10.5
EC	10.5
MCC	q.s
Mg.stearate	5.25
Sodium bicarbonate	35
Talc	5.25
Total weight	**350mg**
Immediate Release Formula (R1)	
RAMOSETRON	1
MCC	Q.S
PVP K 30	3.75
Talc	3
SSG	7.5
Mg.stearate	3.75
Total weight	**100mg**
Total weight of the bilayered tablet: 450mg	

2.2.2. Evaluation parameters

2.2.2.1. Pre-compression studies

Angle of Repose:

The flow property was determined by measuring the Angle of Repose. In order to determine the flow property, the Angle of Repose was determined. It is the maximum angle that can be obtained between the free standing surface of a powder heap and the horizontal [(9)].

Angle of repose= $\tan^{-1}$ (h/r)

Where, h = height r = radius

Bulk density:

Bulk density is ratio of given mass of powder and its bulk volume. Bulk density was determined by measuring the volume of known mass of powder sample that has been passed through the screen in to graduated cylinder or through volume measuring apparatus in to cup [(10)].

Bulk density = M / V_0

Where M= mass of the powder; V_0=bulk volume of the powder.

Tapped density:

A known quantity of powder was transferred to a graduated cylinder and volume V0 was noted. The cylinder fixed to a density determination apparatus, tapped for 200 times then reading was observed. The density is achieved by mechanically tapped by a measuring cylinder containing the powder sample. After observing the initial volume the cylinder is mechanically tapped and volume reading were taken until little further volume changes is observed [(11)].

Tap density = M / V_r

Where M = mass of the powder, V_r = final tapping volume of the powder.

Compressibility index and Hausner ratio:

The compressibility index and hausner ratio may be calculated using measuredvalues of bulk density and tapped density as follows:

Compressibility index = 100 ×{ tapped density - bulk density / bulk density}

Hausner ratio = tapped density / bulk density

2.2.2.2. Post compression studies

Weight variation test

Twenty tablets were weighed individually and the average weight was calculated. The individual tablet weights are then compared to the average weight. Not more than two tablets should differ in their average weight by more than percentages stated in USP. No tablet must differ by more than double the relevant percentage.

Content Uniformity

Randomly select 30 tablets. 10 of these assayed individually. The Tablet pass the test if 9 of the 10 tablets must contain not less than 85% and not more than 115% of the labeled drug content and the 10th tablet may not contain less than 75% and more than 125% of the labeled content. If these conditions are not met, remaining 20 tablets assayed individually and none may fall outside of the 85 to 115% range.

Friability:

A number of tablets are weighed and placed in the apparatus where they are exposed to rolling and repeated shocks as they fall 6 inches in each turn within the apparatus. After four minutes of this treatment or 100 revolutions, the tablets are weighed and the weight compared with the initial weight. The loss due to abrasion is a measure of the tablet friability [(12)].

The percentage friability was determined by the formula:

% friability = $(W_1-W_2) / W_1 X 100$

Drug release

The drug release from the floating and immediate release tablets was investigated in a USP-II (paddle) apparatus, 900 ml of 0.1N HCl (50 rpm, 37°C). At predetermined time intervals, 5-ml samples were withdrawn and take 1ml sample and diluted to 10 ml and then analyzed with UV spectrophotometry at λmax=256nm [(13)].

2.2.3. Drug release kinetics

Zero-Order Kinetics:

Zero order as cumulative amount of Percentage drug released v_s time

$$C = K_0 t$$

Where *K0* is the zero-order rate constant expressed in units of concentration/time and *t* is the time in hours. A graph of concentration vs time would yield a straight line with a slope equal to *K0* and intercept the origin of the axes.

First order kinetics:

First order as log cumulative percentage of log (%) cumulative drug remaining $v_s$time,

$$Log C = Log C_o - k t / 2.303$$

Where $C_0$is the initial concentration of drug, *k* is the first order constant, and *t* is the time.

Higuchi Model:
Higuchi's model as cumulative percentage of drug released v_s square root of time

$$Q = K t_{1/2}$$

Where *K* is the constant reflecting the design variables of the system and *t* is the time in hours. Hence, drug release rate is proportional to the reciprocal of the square root of time.

Korsmayer Peppas equations:
Korsmeyerpeppas equation used to determine the mechanism of drug release form the polymer matrix of the tablet**.** Log cumulative percentage of drug released VS Logtime, and the exponent *n* was calculated through the slope of the straight line.

$$M t / M_{\infty} = K t^{n}$$

Where Mt/M_ is the fractional solute release, *t* is the release time, *K* is a kinetic constant

Hixoncrowell erosion equation:

Hixson-Crowell cube root law, as the cube root of percentage drug remaining vs. time correlated the release from systems with polymer erosion/dissolutionresulting in a change in surface area and diameter of particles or tablets.

$$Q_0^{1/3} - Q_t^{1/3} = kHC_t \ldots\ldots\ldots(4)$$

Where, Qt is the amount of drug released in time t, Q0 is the initial amount of the drug in the tablets, and kHC is the rate constant for the Hixson-Crowell rate equation [(14)].

3. RESULTS AND DISCUSSION:

3.1. Pre compression parameters

The properties like compressibility index, angle of repose and hausner's ratio were calculated. The results are presented in Table 4 & 5. Based on these parameters, it indicates that the flow is good.

Table 4: Pre compression studies of floating layer of HU

Parameter	H1	H2	H3	H4	H5	H6	H7	H8	H9
Angle of repose	$27^0$55'	29^o39'	23^o31'	$28^0$81'	$28^0$65'	$26^0$74'	28^o39'	$21^0$81'	$24^0$81'
Bulk density	0.63	0.55	0.51	0.47	0.60	0.57	0.46	0.42	0.61
Tapped density	0.66	0.63	0.54	0.52	0.64	0.63	0.51	0.53	0.69
%Compressibility Index	4.76	14.54	5.88	10.63	6.66	10.52	10.86	26.19	13.11
Hausner's ratio	1.047	1.14	1.05	1.10	1.06	1.10	1.10	1.15	1.13

Table 5: Pre compression parameters of ramosetron

Formulations	Angle of repose (°)	Bulk Density (g/mL)	Tapped Density (g/mL)	Carr's Index (%)	Hausner'sratio
R1	27.9	0.31	0.35	11.42	1.12
R2	27.13	0.34	0.41	17.07	1.20
R3	26.34	0.31	0.36	13.88	1.16
R4	27.50	0.31	0.37	16.21	1.19
R5	28.4	0.32	0.37	13.51	1.15
R6	25.61	0.35	0.40	12.5	1.14
R7	25.42	0.31	0.36	13.88	1.16
R8	26.35	0.35	0.41	14.63	1.20
R9	28.40	0.32	0.37	13.51	1.15

3.2. Evaluation of physical parameters of tablets:

All formulations were tested for physical parameters like hardness, thickness, weight variation, friability and found to be within the pharmacopoeial limits. The results of the tests were tabulated. The assay of all the formulations was determined and was found to be within the permissible limit. This study indicated that all the prepared formulations were good. The results are displayed in Table 6 & 7.

Table 6: Post compression studies for floating layer of HU

Parameters	H1	H2	H3	H4	H5	H6	H7	H8	H9
Weight variation	350±2.34	354±3.15	361±2.87	358±3.19	355±1.95	348±2.28	360±3.48	353±2.53	359±4.35
Thickness (mm)	3.5±0.4	3.6±0.4	3.3±0.4	3.6±0.4	3.5±0.4	3.5±0.3	3.9±0.4	4.0±0.1	3.8±0.2
Hardness (kg/cm^2)	6.9±1.4	6.4±1.2	6.2±1.2	7.1±0.9	6.4±1.9	6.1±1.7	6.2±1.5	6.3±1.6	6.7±1.4
Friability	0.22±0.2	0.26±0.23	0.25±0.19	0.25±0.26	0.25±0.22	0.22±0.1	0.21±0.4	0.21±0.5	0.21±0.7
Assay	99.91±0.2	99.84±0.4	99.87±0.3	98.88±0.2	99.88±0.3	99.89±0.2	99.88±0.2	99.68±0.2	99.88±0.2

Table 7: Post compression studies for ramosetron immediate release tablets

Formulations	Average weight (mg)	Hardness Kg/cm^2	Thickness (mm)	Friability (%)
R1	100	3.4	2.1	0.29
R2	99	3.5	2.3	0.25
R3	101	3.1	2.5	0.30
R4	100	3.3	2.2	0.41
R5	100	3.1	2.1	0.25
R6	99	3.2	2.3	0.36
R7	102	3.6	2.4	0.52
R8	100	3.5	2.1	0.42
R9	98	3.2	2.2	0.49

3.3. *In vitro* dissolution studies

The formulations H1 to H3 were prepared by using guar gum, the release was found to be 98.7% (3 hrs), 99.58% (6 hrs), and 97.10% (8 hrs) respectively. Formulations H4 to H6 were made by carbopal 34 and release were found to be near to 100% but did not provide the sustained release pattern for 12 hrs. Formulations H7 to H9 were utilizing HPMC K 100 and the percentage of drug release of H9 formulation was found to be 97.52% in 12 hrs. Increasing the concentration level of polymer concentration, the drug release was decreased gradually. Based on studies, 70 mg of HPMC K100 containing formulation (H9) showed the maximum amount of drug release. Whereas, immediate release of ramosetron tablets for 60 min, the formulation R 9 showed highest percentage of drug release. The results were represented in Fig 1 & 2.

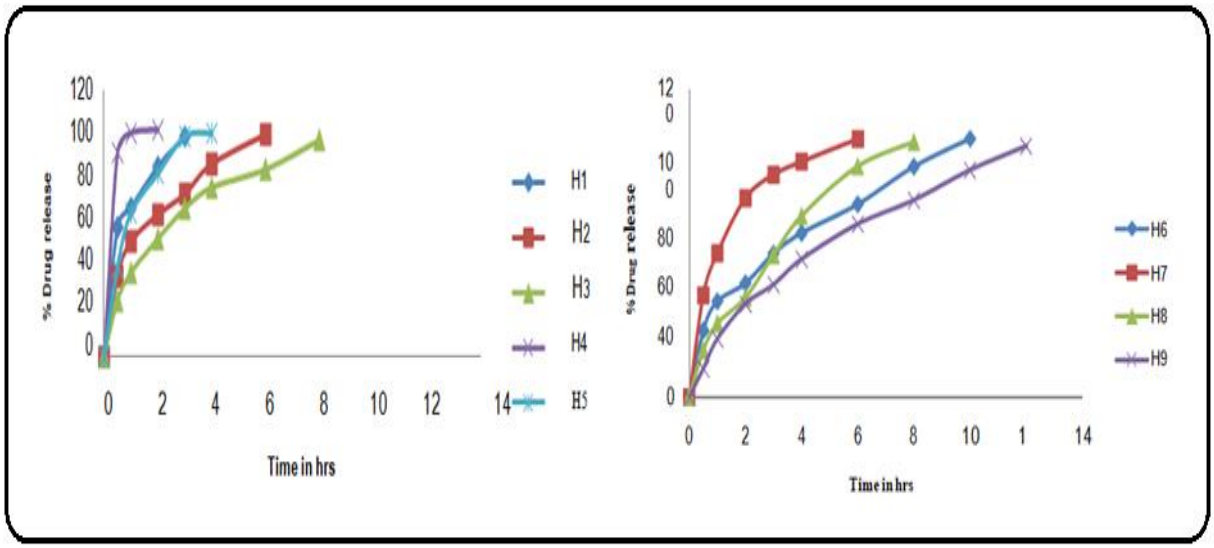

Fig 1: Dissolution profile floating layer of H1-H9 formulations

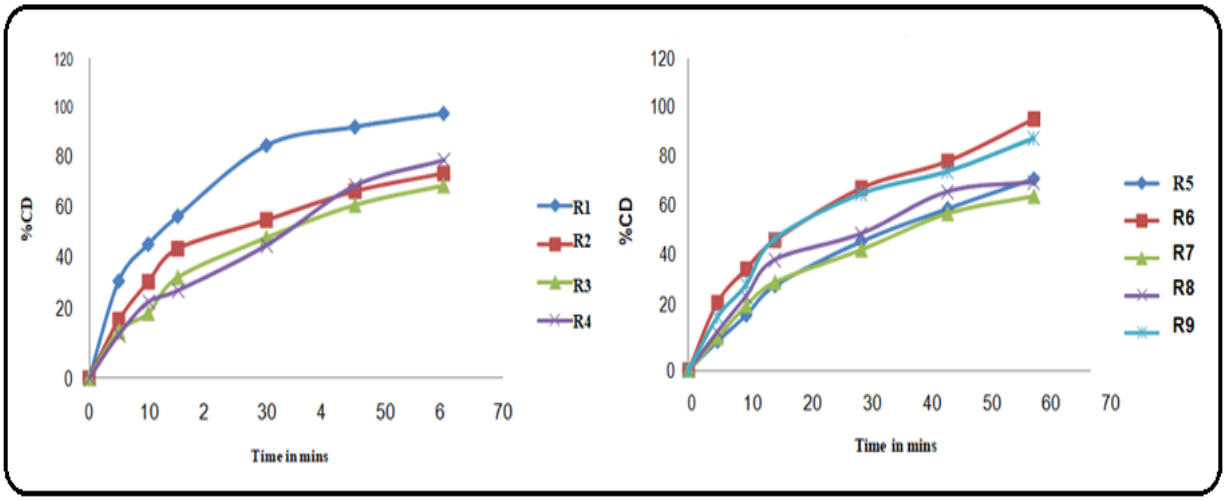

Fig 2: Dissolution profile of IR formulations R1-R9

3.4. Kinetic models

Dissolution data of above two methods was fitted in Zero order, First order and Higuchi equations. The mechanism of drug release was determined by using Higuchi equation. The results are presented in Fig 3.

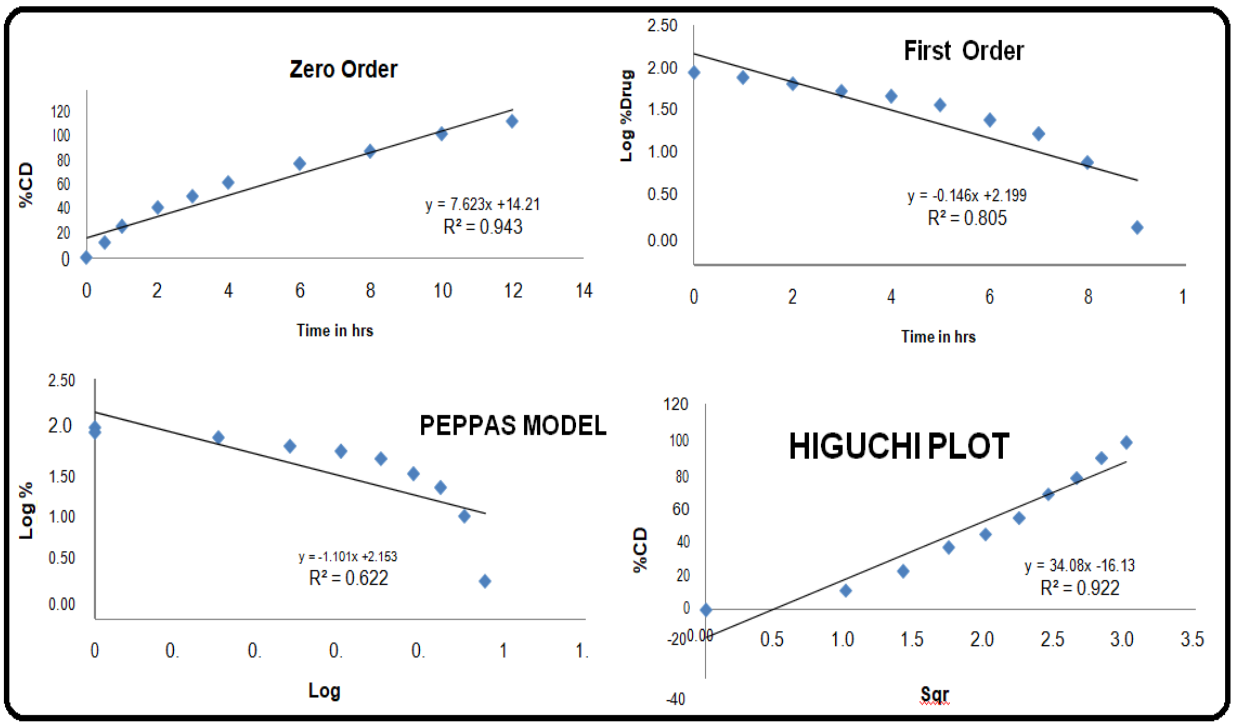

Fig 3: Release kinetics of optimized formulation (F9)

4. CONCLUSION:

The present research was carried out to develop a bilayer tablet of hydroxy urea and ramosetron using super disintegrant for the immediate release layer and guar gum, carbopal 34 and HPMC K100 for the sustained release layer. Bilayer tablets showed the appropriate release effect to provide the loading dose of the drug, followed by sustained release for 12 h, indicating promising potential of the hydroxy urea and ramosetron bilayer tablet as an alternative to the conventional dosage form. However, further clinical studies are needed to explore potential of drugs to achieve maximum bioavailability and reduce the side effects and treatment of disease.

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