ORIGINAL ARTICLE

Design of Modified Release Multiunit Drug Delivery System for the Effective Treatment of Gastroesophageal Diseases using Hot-melt Coating

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Abstract

Aim: The objective of the present investigation involves the design of modified release multiunit drug delivery system for the effective treatment of gastroesophageal diseases (GEDs) using hot-melt coating (HMC) technique. **Materials and Methods:** Ranitidine hydrochloride (R.HCL) pellets were prepared using extrusion-spheronization and coated with different levels of hydrogenated castor oil (HCO) as HMC agent using pan pour method. To achieve the desirable release profile, R.HCL pellets were coated with a hybrid of HCO and sodium lauryl sulfate as a pore former. The pellets were evaluated for micromeritic properties, physicochemical properties, *in vitro* buoyancy study, dissolution study, and stability study. Optimized formulation was selected by comparison of the drug release profiles with theoretical release profile (TRP). **Results:** Formulation R6 with low floating lag time, floating time >12 h, and the drug release profile similar to TRP. Therefore, R6 was selected as optimized formulation and molded into unit dosage form by filling the pellets in hard gelatin capsules. The R6 formulation shows significant performance *in vitro*. Optimized formulation was showed no significant difference in their micromeritic properties, physicochemical properties, *in vitro* buoyancy, and dissolution release after storing under 40°C ± 2°C temperature and 75% ± 5% relative humidity for 3 months. **Conclusion:** This study confirms the modified release potential of HCO by successfully designing of modified multiparticulate drug delivery system of R.HCL using HMC technique. This drug delivery system may prove effective for the treatment of GEDs by sustained drug release in absorption window for prolong period.

Key words: Extrusion-spheronization, hot-melt coating, modified release, gastroesophageal diseases, theoretical release profile

INTRODUCTION

Ranitidine hydrochloride (R.HCL), (E)-1-N'-[2-[[5-[(dimethylamino) methyl]furan-2-yl]methylsulfanyl] ethyl]-1-N-methyl-2-nitroethene-1, 1-diamine hydrochloride, a first generation competitive, and reversible inhibitor of histamine at H_2 histamine receptors. It suppresses the normal secretion of acid by parietal cells and meal-stimulated acid secretion. R.HCL does not reduce the serum Ca^{2+} in hypercalcemic states. The histamine secreted in stomach was blocked from binding on parietal cells of H_2 receptors which are responsible for acid secretion. Gastrin and acetylcholine have a reduced effect on parietal cells when H_2 receptors are blocked. It is widely used in the treatment of duodenal ulcer, gastric ulcer, erosive esophagitis, gastroesophageal reflux disease, and Zollinger–Ellison syndrome.[1] Ranitidine is mainly absorbed from stomach and initial part of small intestine.[2] Oral bioavailability of ranitidine is about 50% due to absorption of the drug in absorption window and colonic metabolism.[3-5]

The design of an oral floating drug delivery system (FDDS) should be primarily aimed to achieve more predictable and increased bioavailability of drugs. The development

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process is precluded by several physiological difficulties, such as an inability to restrain and localize the FDDS within desired regions of the gastrointestinal tract and the highly variable nature of gastric emptying process.[6] Depending on the physiological state of the participant and the design of pharmaceutical formulation, the emptying process can last from a few minutes to 12 h. This variability, in turn, may lead to an unpredictable bioavailability and times to achieve the peak plasma levels since the majority of drugs are preferentially absorbed in the upper part of the small intestine. Thus, control of placement of FDDS in a specific region of the gastrointestinal tract offers numerous advantages, especially for the drugs exhibiting an absorption window in the gastrointestinal tract or drugs with stability problem. Overall, the intimate contact of the FDDS with the absorbing membrane maximizes drug absorption and may also influence the rate of drug absorption. These considerations have led to the development of oral Modified Release Drug Delivery System (MRDDS).[7]

FDDS is one of the approaches for gastroretention. FDDS or hydrodynamically balanced systems have a bulk density (BD) lower than gastric fluids and thus, remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period. While the system is floating on the gastric contents, the drug is released slowly at a pre-determined rate.[8]

Hot-melt coating (HMC) or solvent-free coating methods offer many merits over currently used conventional coating techniques, such as they do not require the use of costly organic solvents. Since there is no solvent to be evaporated, processing times are much shorter. The tedious process of solvent disposal, treatment or recovery associated with organic solvents is eliminated. Since no aqueous medium is used, no risk of bacteriological contamination and hydrolysis of drug, and the process is environment-friendly. The materials used for solvent-free coating techniques are generally waxes that are much cheaper as compared with costly polymers employed in solvent coatings.[9,10] The great versatility of waxes in terms of their solubility and ability to solubilize other excipients make them useful in a variety of formulations for different purposes. Although few, whatever, research that has been performed in HMC employed waxes such as beeswax, cetyl alcohol, and lanolin, which have definite disadvantages such as the ability to demonstrate hypersensitivity or immunogenic responses in certain individuals. Very few studies ever employed hydrogenated castor oil (HCO) as an agent for HMC. Moreover, studies that employed the procedure for preparing MRDDS were normally carried out in coating pan and fluid bed apparatus, which limits the technique as it involves sophistication.[10-12]

The objective of the present investigation was to design MRDDS of R.HCL for the effective treatment of gastroesophageal diseases (GEDs) using HMC technique. Prolonged gastric retention of R.HCL in absorption window improves the bioavailability of the drug. This research work has made a novel approach in the design of MRDDS using HCO as HMC agent.

MATERIALS AND METHODS

Materials

R.HCL was procured from Wockhardt Pharma Ltd., Aurangabad. HCO was purchased from Sree Rayalaseema Alkalies and Allies Pvt. Ltd., Chennai. Microcrystalline cellulose (MCC), non-pareil seeds, talc, and titanium dioxide were gift samples from Themis Laboratories, Mumbai. Sodium bicarbonate, hydroxypropyl methylcellulose (HPMC), sodium lauryl sulfate (SLS), diethyl phthalate (DEP), and polyvinylpyrrolidone K30 (PVP K30) were purchased from S D Fine Chemicals, Mumbai. All the other chemicals and reagents used were of analytical and laboratory grades.

Methods

Construction of theoretical release profile (TRP) of R.HCL.

Calculation of loading dose (D_L): The loading dose is required to give an initial rapid burst of dose so as to attain therapeutic range immediately after dosing.

$$\text{Loading dose } (D_L) = C_{SS\ (Avg)} \times V_d/F$$

Where, D_L is the loading dose of R.HCL, $C_{SS\ (Avg)}$ is average steady state plasma level, V_d is volume of distribution of R.HCL, and F is absolute bioavailability.

$$\text{Loading dose } (D_L) = 0.525 \times 91/0.5 = 95.55 \text{ mg}$$

Maintenance dose (D_M): The therapeutic level is attained with the bursting of loading dose; the maintenance dose is required to maintain the constant level in plasma for desired period.

$$D_M = K_0 \times H$$

Where, H = total desired time for sustained action in hours,

$$\text{Drug availability rate } (K_0) = K_e \times D_L$$

Where, K_e = Elimination rate constant

$$\text{Drug availability rate } (K_0) = 0.198 \times 95.55 = 18.92 \text{ mg/h}$$

Thus, drug availability rate (K_0) is 18.92 mg/h, which should be equal to over-all elimination rate constant so as to maintain steady state plasma concentration.

$$D_M = K_0 \times H = 18.92 \times 12 = 227 \text{ mg}$$

Since peak plasma level is achieved in 2 h, the corrected loading dose can be determined as,

Loading dose (DL*) = DL − ($K_0 \times t_p$) = 57.73 mg

Where, t_p = Peak plasma concentration time.

Total dose (D_T) = D_L* + D_M = 57.73 + 227 = 284.73 mg

Since, the total dose of ranitidine requires for preparing modified release dosage form was round off to 300 mg (≈ 336 mg of R.HCL). Drug delivery system should release 20, 45, 60, 75, 90, and >90% of R.HCL in 2, 4, 6, 8, 10, and 12 h respectively.[13]

Preparation of R.HCL pellets

R.HCL pellets were prepared using extrusion-spheronization technique (Glatt Model P 100). Accurately weighed R.HCL, talc, and MCC were mixed in mini double cone blender (Shakti Lab Model GMP) for 5 min [Table 1]. PVP K30 solution prepared in isopropyl alcohol (5% w/v) was added to above mixture to form a cohesive mass. The coherent mass was passed through axial screw extruder of 16 mesh screen at 100 rpm, and the wet pellets were transferred to spheronizer. The spheronizer was operated at 1000 rpm for 10 min using 1 mm hatch pattern friction. Pellets were dried in hot air oven for 24 h at 60°C. Finally, dried pellets were shifted to collect 16/20 mesh fractions and were used for further coating.[14]

Coating of pellets with effervescent layer and gas entrapment layer

The collected 16/20 mesh fractions of pellets of the drug were coated separately with 10% w/w sodium bicarbonate dispersion using HPMC as a binder. Pellets were dried in hot air oven (Lab Hosp) at 60°C for about 2 h.[15]

HMC of R.HCL pellets

The HMC of R.HCL pellets was carried out in modified coating pan. The coating pan was operated at 30 rpm. R.HCL pellets about 0.5 kg of 16/20 mesh size were loaded in coating pan and warmed to 60°C with the convection heater. HCO was melted by means of heating at 80°C and used for coating at different levels. HCO also has been employed for coating with varying quantity of SLS to achieve desirable release profile [Table 2]. SLS and DEP were used as pore former and plasticizer, respectively. The coating mass was poured slowly onto the surface of pellets for about 30 min. Coated pellets were further rolled in coating pan for 10 min, and the temperature was allow to reduced about room temperature. Hot-melt coated pellets were removed from coating pan and cured at 30°C for 24 h.[16]

Table 1: Formulation of R.HCL pellets

S. No.	Ingredient	Quantity (mg)
1	R.HCL	336
2	MCC	14
3	PVP K30 solution	Q.S.

R.HCL: Ranitidine hydrochloride, MCC: Microcrystalline cellulose, PVP K30: Polyvinylpyrrolidone K30, Q.S: Quantity sufficient

Table 2: HMC composition for R.HCL pellets

Formulation*	R1	R2	R3	R4	R5	R6
HCO	15	22	30	29.75	29.50	29
SLS	-	-	-	0.25	0.50	1
Titanium dioxide	1	1	1	1	1	1
DEP	1.5	2	3	3	3	3

*Formula for coating the ranitidine pellets equivalent to 336 mg of R.HCL. All weights were taken in mg. R.HCL: Ranitidine hydrochloride, HMC: Hot-melt coating, HCO: Hydrogenated castor oil, SLS: Sodium lauryl sulfate, DEP: Diethyl phthalate

Molding of R.HCL pellets into unit dosage form

Accurately weighed quantity of pellets equivalent to 336 mg of R.HCL was filled into hard gelatin capsules to convert into unit dosage form.[16]

EVALUATION OF PELLETS

Micromeretic properties of pellets

Angle of repose (AR)

Accurately weighed 50 g of pellets were poured gently through glass funnel on the graph paper. The height of the pile and diameter were noted. The calculation of angle of repose (AR) was carried out using the following Equation (1).[17]

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

Bulk Density (BD)

Accurately weighed 25 g of pellets of 16/20 mesh were poured gently through glass funnel into 100 ml calibrated measuring cylinder. The surface was carefully made smooth without application of pressure with a glass rod. The volume occupied by pellets was recorded, and BD (g/ml) was calculated using the following Equation (2).[17]

Bulk density = Weight of pellets/Bulk volume of pellets (2)

Tapped density (TD)

TD was determined similarly to that of the BD. However, final volume was measured after tapping the cylinder from

3″ until constant volume was obtained using (Electrolab, Model etd-1020) TD apparatus. The volume occupied by sample was recorded, and TD (g/ml) was calculated using the following Equation (3).[17]

Tapped density = Weight of pellets/Tapped volume (3)

Compressibility index (CI)

The morphology of pellets and total structure can change in any variation in formulation or material properties, affecting porosity, which is considered to have a great influence on coating, flow, and packing during tablet or capsule filling. It also influences the rate of release of drug from pellets by affecting the capillary action of dissolved drug. From the BD and TD data, the CI was calculated using the following Equation (4).[17]

Compressibility index = 100 × (Tapped density − Bulk density)/Tapped density (4)

Hausner's ratio (HR)

HR was calculated from BD and TD data using the following Equation (5).[17]

Hausner's ratio = Tapped density/Bulk density (5)

Physicochemical properties of pellets

Photomicrography

Stereomicrographs of uncoated and HMC pellets were taken using Intel play digital microscope QX3 attached to a personal computer. The photographs were used to examine the uniformity of coating and surface of pellets after coating.[16]

Hardness and friability

The hardness of pellets was examined by Veego hardness tester (Veego Scientific, Model HT-1) and noted. For the friability study, accurately weighed 10 g of pellets (initial weight) were placed on sieve having 0.85 mm aperture with 25 glass beads of 3 mm diameter and then both were placed in Roche friabilator (Veego Scientific, VFT-2D) for 100 revolutions at 25 rpm speed. The pellets were collected and placed on the sieve with 0.85 mm aperture. The smaller particles were allowed to pass through the sieve and pellets were reweighed (final weight). The % friability was determined as percentage loss of mass of pellets after the test was calculated using the following Equation (6).[17]

% Friability = 100 × (Initial weight − Final weight)/Initial weight (6)

Size distribution

The size distribution of pellets was carried out using sieve shaker (Electrolab, Model EMS-8) and set of four active standard test method sieves (#14, #16, #18, and #20) for 5 min. The size distribution of pellets expresses the efficiency of the process of manufacturing the uniform size pellets. The mean pellet size was calculated using the following Equation (7).[17]

Mean pellet size (d_{avg}) = (∑ % retained × Average sieve aperture)/100 (7)

In vitro buoyancy study

Floating abilities of coated pellets were determined using beaker containing 100 mL of 0.1N hydrochloric acid (HCL) maintaining the temperature 37°C ± 0.5°C in water bath. Twenty pellets were placed slowly in the medium. The floating lag time (FLT) and floating time (FT) of pellets were determined by visual observation.[18]

Dissolution study

In vitro dissolution study was carried out using the United State Pharmacopoeia (USP) dissolution apparatus II (Electrolab, TDT-08L) in 900 mL of 0.1N HCL at 37°C ± 0.5°C and 50 rpm using sample size (n = 6). The samples were withdrawn for 12 h at pre-determined time interval and filtered using 0.45 µ membrane filter, and absorbance were recorded using UV-visible spectrophotometer (Shimadzu, UV 1601) for the formulations at absorption maxima (λ_{max}) 313 nm.[19] Selection of optimized formulation was performed by comparing dissolution profiles of all formulation with TRP using difference factor (f_1) and similarity factor (f_2).[20-22]

Kinetic analysis

The dissolution profile of all the batches was fitted in zero order, first order, Higuchi, Hixson–Crowell, and Korsmeyer–Peppas models to ascertain the drug release mechanism using PCP dissolution software version 2.08. Dissolution model with the high correlation coefficient was considered to be the best model.[20]

Drug content

The pellets were powdered and powder equivalent to 336 mg of R.HCL was accurately weighed, transferred into 100 mL volumetric flasks, and dissolved in 0.1N HCL, and the volume was made up to the mark using 0.1N HCL. The solution in the volumetric flask was filtered, and suitable dilution was made. These solutions containing R.HCL were analyzed at 313 nm using UV-visible spectrophotometer.[19]

Stability studies of pellets

The pellets of optimized unit dose formulation of R.HCL were placed in amber-colored bottles. The

bottles were wrapped with aluminum foils and stored at the temperature of 40°C ± 2°C and relative humidity (RH) 75% ± 5% for 6 months in the stability chamber (Remi Laboratory Instrument CHM-6S [GMP]). These formulations were evaluated for any changes in micromeritic, physicochemical, floating, and *in vitro* drug release properties after 6 months. The result obtained was compared with data obtained for zero time and room temperature (28°C ± 2°C) and RH (42% ± 2%). The plot of percentage drug releases against time (h) on the day of preparation of formulation and after 6 months for stability study was plotted.[23]

RESULTS

Micromeritic properties of pellets

The micromeritic properties of pellets were determined from the values of AR, HR, and CI [Table 3]. The values of AR, CI, and HR for uncoated pellets were 28.32°, 11.557%, and 1.131%, respectively. The values of AR, CI, and HR for coated pellets were ranging from 18.57-25.03°, 5.368-9.416%, and 1.056-1.104, respectively.

Physicochemical properties of pellets

The morphology of uncoated and coated pellets was confirmed using stereomicrography [Figure 1]. The mean pellet size for uncoated and coated pellets was found to be 845 and 852-895 µ, respectively. The hardness of uncoated pellets was found to be 2.45 kg/cm^2 and the hardness of coated pellets was found to be 2.65-3.10 kg/cm^2. The % friability for uncoated pellets was found to be 0.358% and % friability for coated pellets was found to be 0.168-0.248%. The drug content in uncoated pellets was found to be 100.65% and drug content in coated pellets was found to be 98.86-101.35% [Table 4].

In vitro buoyancy study

Floating ability of pellets was expressed by FLT and FT. Sodium bicarbonate liberates CO_2 in the presence of HCL and the generated gas was trapped and protected within the hydrophilic structure formed by hydration of the HPMC; thus, decreasing the density of the pellets below 1 g/mL and the pellets become buoyant. The optimized concentration of sodium bicarbonate was used for all the R.HCL floating pellets. All floating pellets had FLT in the range of 3-41 min. The TFT was found to be in the range of 10-26 h, indicating a stable hydrophobic layer formation by HCO, and sodium bicarbonate that persists for a longer time. The results of the FLT and FT for the different floating pellet formulations are given in Table 4.

Dissolution study

As the coating level of HCO increases, it forms the dense network structure that retards the drug release from the pellets. Figure 2 confirms the sustain release potential of HCO. The modified release ability of HCO was depends on physicochemical properties of drug, coating level, and coating composition. The 5% and 7.5% coating level of HCO, respectively, in the R1 and R2 formulations are unable to retard the drug release up to 12 h. At 10% coating level of HCO formulation R3 releases about 49.66% of R.HCL in 12 h.

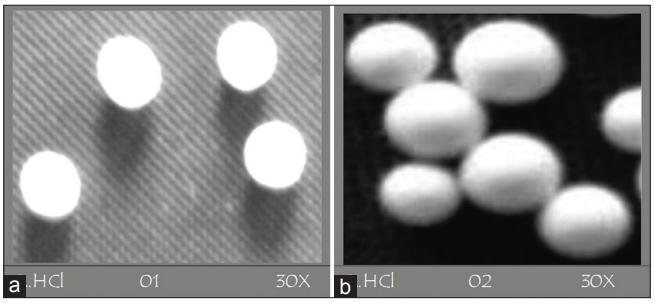

Figure 1: Photomicrograph (a) uncoated and (b) coated ranitidine hydrochloride pellets

Table 3: Micromeretic properties of R.HCL pellets

Formulation	Micromeretic properties†				
	AR (°)	BD (g/ml)	TD (g/ml)	CI (%)	HR
R1	25.03	0.683±0.002	0.754±0.001	9.416±0.002	1.104±0.001
R2	23.48	0.718±0.001	0.754±0.002	7.949±0.002	1.086±0.002
R3	20.66	0.724±0.003	0.785±0.001	7.771±0.004	1.084±0.003
R4	20.12	0.744±0.003	0.795±0.003	6.415±0.003	1.068±0.002
R5	19.78	0.746±0.002	0.795±0.003	6.163±0.002	1.065±0.001
R6	18.57	0.758±0.002	0.801±0.002	5.368±0.001	1.056±0.001
R0	28.32	0.704±0.002	0.796±0.002	11.557±0.004	1.131±0.001
R6S	18.61	0.766±0.002	0.804±0.003	4.726±0.005	1.049±0.001

†Values indicate (mean±SD) where sample were analyzed three times. R0 indicate uncoated pellets of R.HCL. R6S indicates R6 pellets stored for stability study as per ICH guidelines. R.HCL: Ranitidine hydrochloride, AR: Angle of repose, BD: Bulk density, TD: Tapped density, CI: Compressibility index, HR: Hausner's ratio, SD: Standard deviation

For improving the release rate from R3 formulation, HCO was mixed with varying amounts of SLS as a pore former to achieve TRP. Using desirable coating level and pore former in coating composition, the desirable release profile was obtained. The concentration of pore former used was a critical value; therefore, care must be taken while using the same.

Kinetic analysis

Dissolution study data were fitted in various mathematical models [Table 5]. Release profiles of formulation R1 and R2 fit in Higuchi model, whereas release profile of formulation R3, R4, R5, and R6 were fits into zero-order model. The "*n*" values of Korsmeyer–Peppas model were between 0.5 and 1for the prepared formulations.

Stability studies of pellets

The optimized formulation stored for stability study was evaluated for micromeritic, physicochemical, floating, and drug release properties [Tables 3 and 4, Figure 3].

DISCUSSION

The micromeritic properties of the pellets were shown good to excellent flow property. The percent yield of coated pellets was excellent since almost no agglomeration was observed during the HMC. As the coating composition was non-tacky, due to the presence of HCO it facilitates the free-flowing of pellets. The pellets prepared after HMC were with excellent morphology and even surface. Stereomicrography confirmed consistency and nature of coating of pellets. The coating can be performed with ease and rapidly. The drug content, hardness, and friability of pellet formulations were found within the USP limits. The HMC improves the hardness and reduce the friability of the coated pellets. Both FLT and FT were depends on the level of HCO and amount of SLS used in coating composition. FLT was found to be a function of nature of coat and coating composition.

Formulation R6 release profile showed similarity with TRP. The difference factor (f_1) and similarity factor (f_2) values were found to be between 3.21 and 82.94, respectively, for R6 formulation. Hence, R6 was selected as optimized formulation. The "*n*" values of Korsmeyer–Peppas model indicates the drug release was taking place mostly by anomalous transport (i.e., by non-Fickian diffusion) hence, drug release mechanism from pellets was diffusion coupled with erosion except for R3 and R4 formulations. In case of R3 and R4 formulations, the drug release mechanism was exclusively by erosion mechanism that may be due to high levels of absolute HCO. The R6 formulation was found to be stable at accelerated condition as per ICH guideline for 6 months.

Table 4: Physicochemical and floating properties of R.HCL pellets

Formulation	Physicochemical properties				Floating ability	
	Mean size (μ)	Hardness‡ (kg/cm²)	Friability‡ (%)	Drug content‡ (%)	FLT (min)	FT (hr)
R1	852	2.65±0.05	0.248±0.001	98.86±1.26	12	10
R2	858	2.80±0.10	0.232±0.002	100.26±2.06	28	14
R3	876	3.05±0.05	0.168±0.001	99.54±0.84	41	26
R4	880	3.10±0.10	0.215±0.003	101.35±1.98	14	21
R5	882	3.10±0.15	0.228±0.004	99.02±3.13	9	16
R6	895	3.05±0.15	0.235±0.003	98.91±0.57	3	12
R0	845	2.45±0.10	0.358±0.005	100.65±2.53	–	–
R6S	890	3.05±0.10	0.228±0.004	98.68±0.21	4	14

‡Values indicate (mean±SD) where sample were analyzed triplicate. R.HCL: Ranitidine hydrochloride, FLT: Floating lag time, FT: Floating time, SD: Standard deviation

Table 5: Kinetic analysis

Formulation	Zero order		First order		Higuchi	Korsmeyer–Peppas		Hixson–Crowell
	K_0	R^2	K_1	R^2	R^2	R^2	"*n*"	R^2
R1	5.6067	0.7015	0.2019	0.5566	0.8710•	0.6390	0.7212	0.6183
R2	8.3431	0.9457	0.2577	0.7235	0.9874•	0.7251	0.8631	0.8533
R3	4.0912	0.9984•	0.2806	0.8925	0.9660	0.6970	1.1260	0.9523
R4	5.3195	0.9961•	0.2697	0.8556	0.9649	0.6939	1.0172	0.9439
R5	6.6906	0.9983•	0.2801	0.8228	0.9724	0.7167	0.9589	0.9428
R6	8.5147	0.9960•	0.2937	0.8327	0.9751	0.7518	0.9202	0.9401

•Indicates best fitted kinetic model, K_0: Zero order rate constant, K_1: First order rate constant, R_2: Regression coefficient, n: time exponent for Korsmeyer-Peppas model

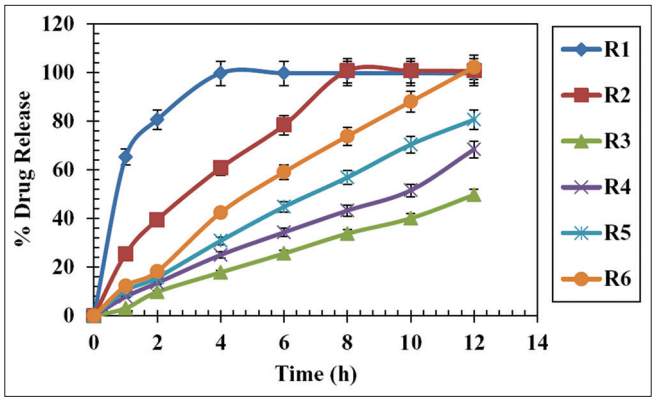

Figure 2: Dissolution study of hot-melt coated ranitidine hydrochloride formulations

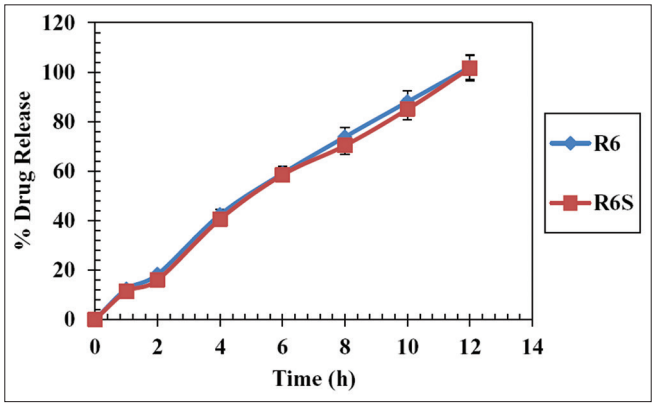

Figure 3: Comparison of release profile of optimized formulation with stability batch

CONCLUSIONS

The R.HCL pellets were successfully prepared by extrusion-spheronization technique. The pellets prepared by HMC were spherical in shape, smooth surface and narrow pellet size distribution was achieved. The pellets were coated with HCO using HMC in a modified conventional pan coater and proven to be successful. HMC technique presents a simple, cost-effective, fast, and effortless choice compared to conventional coating methods where solvent evaporation and recovery could become very expensive and time-consuming.

The results revealed that the HCO alone in different levels was unable to attain the desirable release profile of the drug from formulations. Therefore, to achieve the desirable release profile, the pore former like SLS in different amount used in coating composition. Formulation R6 was selected as optimized formulation using difference (f_1) and similarity factor (f_2). Optimized formulation stored according to the ICH guidelines was found to be stable for 6 months. HMC was proved to be economic way of manufacturing modified release multiunit drug delivery system. From kinetic analysis, drug release from the hot-melt coated pellets was primarily controlled by drug diffusion coupled with erosion and extensively by erosion mechanism may be due to hydrophobic nature of coat. Thus, the present MRDDS may prove to be very effective therapy for treatment of GEDs by release of the drug at pre-determined rate in absorption window for prolong period. A further *in vivo* study has to be carried out to assess the bioavailability of the drug from the modified release multiunit drug delivery system.

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