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Original Article

FLOATING RANITIDINE MICROPARTICULATES: DEVELOPMENT AND *IN VITRO* EVALUATION

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ABSTRACT

Objective: Rapid and inconsistent gastrointestinal tract (GIT) transit could result in reduced drug efficiency and the need for frequent dose administration, which usually result in patients' incompliance. Ranitidine hydrochloride (RH), as a model drug is freely soluble, moisture sensitive drug with a short biological half-life (~2.5-3 h) and narrow absorption window in the initial part of the small intestine. The present study aimed to develop ranitidine floating multi-particulates (RFM) using melt granulation technique and investigation of the effect of lipids and additives on the physicochemical properties.

Methods: RFM were prepared using Compritol® 888 ATO, glyceryl behenate, Cutina® HR, Cutina® GMS, hydrogenated castor oil, glyceryl monostearate, and beeswax as lipids and ethyl cellulose, Povidone® K 90 and Aerosil® 200 as release modifiers. The effect of the preparation method and additives, as well as storage for 6 mo at 40 °C, on floating and release characteristics were evaluated.

Results: Size distribution indicated that the prepared formulations exhibited reasonably small floating micro particulates; more than 90% of the prepared microparticles were less than 710 µm. Hausner ratios and Carr's compressibility indices ranged from 1.17 to 1.29% and 14.54 to 22.4 %, respectively, and the angle of repose values was ≤40 °, indicating good flow properties. RFM containing Compritol® showed a relatively higher release properties compared to hydrogenated castor oil. Increasing the proportion of the fatty component was accompanied by retardation in RH release. The tested additives (PVP, ethyl cellulose, Aerosil®) resulted in different degrees of retardation of drug release. The percent-floating of RFM was almost 100% in all formulations with the exception of formulations prepared using glyceryl monostearate. FT-IR and DSC studies indicated the compatibility of the excipients with RH. Stability results revealed an insignificant change in RFM properties over 6 mo.

Conclusion: The prepared microparticles exhibited optimum particle size, good compressibility, and flow properties. RFM containing Compritol® showed a relatively higher release properties compared to hydrogenated castor oil. Increasing the proportion of the fatty component was accompanied by retardation in RH release. The percent-floating of RFM was almost 100% in most formulations. FT-IR and DSC indicated good compatibility of the excipients with RH and insignificant change in RFM properties over 6 mo's storage.

Keywords: Floating Ranitidine Micro-particulates (RFM), Melt granulation technique

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INTRODUCTION

Although tablets are widely used as a dosage form for several advantages, some drugs are not appropriately formulated as tablets. This may be due to poor bioavailability of some drugs, resulting from incomplete absorption in the gastrointestinal tract (GIT) or such drugs are suffering from narrow absorption window in the upper GIT. Accordingly, rapid and inconsistent GIT transit could result in reduced drug efficiency and thereby increase the need for frequent dose administration, resulting in patients' incompliance. Ranitidine hydrochloride (RH) is freely soluble, moisture sensitive drug with a short biological half-life (~2.5-3 h) and limited absorption from the initial part of the small intestine and shows 50% absolute bioavailability [1, 2], and therefore, is a good candidate representing such class of drugs.

The pharmaceutical research attempted to develop gastro-retentive dosage forms (GRDF) to prolong the gastric residence time of this class of drugs, and hence decreasing dose frequency [3]. One of the proposed mechanisms to achieve such objective is the low-density GRDF, which remains buoyant above the gastric secretions for sufficient time to ensure sustained release of the drug [4, 5].

Melt granulation is one of the most widely applied processing techniques in the pharmaceutical manufacturing operations, which has been successfully applied for the formulation of GRDF, e. g. [6]. Melt granulation is a process by which granules are obtained by the addition of either a molten binder or a solid binder which melts during the process. It is also called melt agglomeration and thermoplastic granulation [7]. The absence of water in the agglomeration process makes this approach quite valuable for moisture-sensitive and thermolabile materials [8]. Due to the inert nature of binders used in this technique, formulations are expected to be more stable and less sensitive to pH change.

Among the systems formulated by melt granulation, multi-particulate systems are used most commonly and can offer many unique advantages. Compared to single-unit dosage forms, such as matrix tablets, multi-particulate dosage forms distribute evenly in the GI track and can release drug substances in a uniform and continuous manner. They offer both formulation flexibility and good *in vivo* performance [9]. Multiparticulate dosage forms can also avoid dose dumping, minimize unit to unit variation, include particles with different release rates in one drug product, offer more reproducible release due to less variation in GIT transit time, reduce variation due to GIT condition or food effect and minimize GIT irritation [10]. Ranitidine hydrochloride was considered a good candidate for formulation in gastro-retentive sustained release floating micro particulates because of its narrow absorption window, as it is mainly absorbed in the proximal areas of the gastrointestinal tract [11, 12]. Hence, conventional sustained-release dosage form reaches the colon, where it gets metabolized, resulting in low absorption and poor bioavailability (52%) [1, 2].

Therefore, the aims of this study were a) to develop ranitidine hydrochloride floating multi-particulates using melt granulation technique under different formulation conditions and b) to study the different factors affecting the physicochemical properties of the prepared ranitidine micro particulates.

MATERIALS AND METHODS

Materials

Ranitidine hydrochloride (RH) (SMS pharmaceuticals, India); povidone K 90 (BASF, Germany); Compritol® 888 ATO and glyceryl behenate (Gattefosse, Saint-Priest, France); Aerosil® 200, Cutina® HR, hydrogenated castor oil and Cutina® GMS, and glyceryl monostearate (Cognis, France); beeswax (Kahil, India). All other reagents were analytical reagent grade.

Table 1: Formulation ingredients of ranitidine hydrochloride floating micro particulates (mg)

Formulation	Ranitidine HCl	Compritol 888 ATO	Cutina HR	Cutina GMS	Aerosil 200	PVP K 90	Ethyl cellulose	Total weight
A1	336	672	------		------	-----	------	1008
A2	336	840	------		------	-----	------	1176
A3	336	1008	------		------	-----	------	1344
G1	336	------	------	1008	------	-----	------	1344
H1	336	------	672		------	-----	------	1008
H2	336	------	840		------	-----	------	1176
H3	336	------	1008		------	-----	------	1344
H4	336	------	1008		------	------	168	1512
H5	336	------	1008		------	-----	336	1680
H6	336	------	1008		------	336	------	1680
H7	336	------	1008		100.8	-----	------	1444.8
H8	336	------	1008		100.8	336	------	1780.8
H9*	336	------	1008		100.8	-----	------	1444.8
H10*	336	------	1008		100.8	-----	------	1444.8

*) Different methods of preparation

Equipment

Mettler Toledo electric balance, model MS 104S/01 (Mettler Toledo, Switzerland); Hanson dissolution tester, model SR8-Plus (Hanson, USA); magnetic stirrer (IKA Labortechnik, Germany); Shimadzu Spectrophotometer, model UV-2450 UV-VISIBLE spectrophotometer and Fourier Transform Infrared spectrophotometer, model FT-IR-8400 (Shimadzu, Japan); Heraeus oven, model UT 6200; (Heraeus, Germany); Stability cabinet (Luwa Environmental Specialties LLC, USA); Microscope connected with digital camera (Microvision, France); Scanning electron microscope, model JSM-5300 and ion sputtering device, model JFC-1100E (Jeol, Japan).

Preparation of ranitidine hydrochloride floating micro particulates (RFM)

A total of 12 formulations were prepared according to the following procedure. A calculated amount of the selected lipid was melted in a stainless steel pan kept in an oven at 5 °C above its melting point. RH was sieved from 500 µm sieve and mixed with other excipients in a plastic bag for 3 min, then added to the molten lipid. The mixture was mixed using spatula until homogeneity is reached then mixing was continued till the mass congealed and reached room temperature. The mass was then sieved (850 µm) and the granules were then collected and kept in airtight glass bottles with a desiccant at room temperature. The drug to lipid ratios used to prepare the different formulations were 1:2, 1:2.5 and 1:3. Different release retarding agents were added (Aerosil® 200, PVP k90 and ethyl cellulose) with different drug ratios; 0.3:1, 0.5:1 and 1:1 (table 1).

The effect of inclusion of Aerosil® in RFM was investigated following different techniques. H7 was produced using the same procedure as other formulations, while in H9 Cutina® HR was mixed with previously sieved Aerosil® 200, and then melted together forming a gel mass. Subsequently, pre-sieved ranitidine hydrochloride was added and granulated, and then sieved from 850-micron sieve. H10 was prepared by sieving Aerosil® 200 through 250 µm sieve and separately sieve ranitidine hydrochloride from 710 µm sieve. Subsequently, mixing both of them for 3 min, re-sieving from 500 µm sieve, and finally granulation using melted Cutina® HR followed by sieving from 850 µm sieve.

Characterization of micro-particulates

Sieve analysis

Ranitidine hydrochloride micro particulates (RHM) were subjected to shaking using a set of descending sieves till constant weight of micro-particulates is present on each sieve. RHM collected on each sieve were accurately weighed and the percent weights of RHM retained in each range were computed to characterize the size distribution of the formed microparticulate.

$$\% \text{ Weight of RHM} = \frac{\text{Weight of RHM in this size range}}{\text{Total weight of RHM}} \text{ X } 100$$

Bulk density (ρ_{bulk})

It is the ratio of the total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder into a measuring cylinder and the volume was noted. It is calculated as follows and expressed in g/ml.

$$\rho_{bulk} = (M)/(V0)$$

Where M is the mass of powder and Vo is the bulk volume of the powder.

Tapped density (ρ_{tapped})

It is the ratio of the total mass of powder to the tapped volume of powder. The tapped volume was measured by tapping the powder to constant volume [13]. It is calculated as follows and expressed in g/ml.

$$\rho_{tapped} = (M)/(Vt)$$

Where M is the mass of powder and V_t is the tapped volume of the powder.

Angle of repose

The powder mixture was allowed to flow through a funnel fixed to a stand at a definite height. The angle of repose was then calculated by measuring the height and radius of the heap of the powder formed. The angle of repose θ was calculated from the following equation:

$$\theta = \tan^{-1}\left(\frac{h}{r}\right)$$

Where h is the height of the granules forming the cone (cm) and r is the radius of the granules base in (cm).

Carr's compressibility index and Hausner ratio

The compressibility index and the Hausner ratio were determined by measuring both the bulk volume and the tapped volume of powder. The compressibility index and Hausner ratio indicate the ease with which a material can be induced to flow and may be calculated using measured values for bulk density (ρ_{bulk}) and tapped density (ρ_{tapped}) as follows [13]:

$$\text{Compressibility Index} = 100 \times \left(\frac{\rho_{tapped} - \rho_{bulk}}{\rho_{tapped}}\right)$$

$$\text{Hausner Ratio} = \left(\frac{\rho \text{ tapped}}{\rho \text{ bulk}}\right)$$

Where ρ_{tapped} and ρ_{bulk} are the tapped and bulk density, respectively.

Ranitidine hydrochloride content

An accurate quantity of RFM, equivalent to 5 mg ranitidine hydrochloride was transferred to 500 ml volumetric flask. About 200

ml of water was added and heated to 80˚C with mixing for 30 min, allowed to cool to room temperature while sonicated for another 30 min. The drug solution was completed to 500 ml with water, and the solution was filtered through Whatman filter paper no. 50. The sample was analyzed for drug content by UV spectrophotometry at 313 nm, and the concentrations of ranitidine hydrochloride were determined by using the equation:

$$\% - \text{Drug content} = \frac{\{\text{Drug content (mg)} * 100\}}{\text{Label claim (mg)}}$$

In vitro release study

In vitro release tests were carried out using USP dissolution tester apparatus II (rotating paddle). An accurately weighed amount of RH-loaded micro particulates equivalent to 336 mg RH was added to 900 ml 0.1 N HCl release medium kept at 37±0.5˚C and stirred at 50 rpm. Samples (15 ml each) were withdrawn at predetermined time intervals (1, 2, 4, 6 and 8 h) and filtered using Whatman filter paper no. 50. Each sample was replaced by an equivalent amount of blank dissolution medium maintained at 37 ˚C. The samples were analyzed photometrically at 314 nm. Ranitidine hydrochloride concentration was computed using a standard calibration curve. All release tests were run in triplicates and data were recorded as the mean values±SD.

Evaluation of drug release

Percentage dissolution efficiency (%DE) of a pharmaceutical dosage form can be used to characterize drug release profiles. DE is defined as the area under the dissolution curve up to a certain time, t, expressed as a percentage of the area of the rectangle described by 100% dissolution. DE can be calculated by the following equation:

$$\%\text{DE} = \frac{\int_0^t y \times \mathrm{d}t}{y_{100} \times t} \times 100$$

where y is the %-drug dissolved at time t [14]. In this study, all dissolution efficiencies were obtained with t equal to 8 h. The areas under the curve (AUC) were calculated for each dissolution profile by the trapezoidal method. It is generally preferable to choose a time interval corresponding to 70–90% dissolution unless one wishes to compare an early part of the dissolution curve. Normally t_1=0 for tablets or granules where there is no lag phase. For a capsule product, t1 can be set to the period corresponding to the disintegration of the capsule shell.

In vitro buoyancy studies

The floating abilities of micro-particulates were determined by adding an accurately weighed 100 mg micro particulates in 20 ml pre-warmed 0.1 N HCl containing 0.1 M NaCl, followed by shaking horizontally at a speed of 100 cycles/min using a mechanical shaker apparatus for 12 h at 37 ˚C [15]. The percent-floating micro particulates was calculated by dividing the number of floating micro particulates (nt) by the initial total number tested (n initial) as follows:

$$\frac{n_t}{n_{initial}} \times 100$$

Where n_t is the number of floating micro particulates, and $n_{initial}$ is the total number of micro-particulates.

Scanning electron microscopy (SEM)

The surface morphology of selected beads was visualized by scanning electron microscopy. The sample for SEM was prepared by sticking the beads on a double-sided adhesive tape, stuck to an aluminum stub. The stubs were then coated with a thin layer of gold (~300A°) for 30 seconds at 30 W. The samples were then randomly scanned with 25Kv power, using magnifications from 150 to 2000 times.

Differential scanning calorimetry (DSC)

The DSC measurements were performed using 3 mg samples placed in sealed aluminum pans, before heating under nitrogen flow (20 ml/min) at heating rate 10˚C/min, over the temperature range of 35˚C to 300 ˚C. An empty aluminum pan was used as a reference. DSC of the pure ranitidine hydrochloride, lipids (hydrogenated castor oil or glyceryl behenate), and floating micro particulates were compared with each other.

Infrared spectroscopy

The IR spectra were performed between 3000 and 400 cm^{-1} using KBr disks (about 2 mg sample in 200 mg KBr). Acquired spectra were first corrected for background based on the signal recorded for the same KBr alone. The examination was performed for pure ranitidine hydrochloride, selected lipids, selected examples of floating micro particulates.

Stability studies

Samples of selected formulations were packed in a sealed HDPE bottles with a desiccant, packed into aluminum pouch then were stored in stability chambers at 40˚C and relative humidity 75%. The samples were withdrawn periodically and evaluated for the drug content, *in vitro* drug release, and *in vitro* buoyancy using the same methods previously described.

RESULTS AND DISCUSSION

Preparation of ranitidine hydrochloride floating micro particulates

In the preliminary studies beeswax and stearic acid failed to produce solid multi-particulates, forming instead a sticky mass that clogs the sieve pores during sieving process. Based on preliminary studies, Cutina® GMS, Cutina® HR, and Compritol® ATO 888 were selected as the lipid-bases for further studies.

Particle sizes analysis

Results of size analysis of RFM are listed in table 2. It is obvious from these results that 90% or more of the prepared micro particulates have the particle size of less than 710 µm. The cumulative %-undersize distribution data are summarized in table 3. More than 50% of the floating micro particulates were less than 355 µm and from 75% to 85% were<500.

Table 2: Size distributions (%) of ranitidine hydrochloride microparticulates prepared by melt granulation method (n=3) (average±SD)

Formula	<0.106 mm	0.106-0.355 mm	0.355-0.5 mm	0.5-0.71 mm	>0.710 mm
H1	26.0±0.26	27.4±0.26	22.1±0.17	16.2±0.13	4.9±0.09
H2	27.1±0.17	27.2±0.26	21.8±0.1	15.3±0.05	6.0±0.05
H3	32.7±1.05	33.8±0.17	17.2±0.09	8.8±0.04	1.7±0.04
H4	25.6±0.3	33.09±0.1	17.2±0.08	14.33±0.05	4.0±0.18
H5	26.2±0.2	34. 7±0.1	20.5±0.07	9.7±0.04	2.8±0.06
H6	29.1±0.26	32.4±0.1	21.4±0.12	11.3±0.05	3.7±0.06
H7	19.9±0.17	35.0±0.2	24.1±0.09	14.2±0.03	4.9±0.04
H8	24.7±0.26	31.6±0.17	24.0±0.11	14.1±0.12	3.0±0.11
H9	21.4±0.4	32.1±0.38	22.9±0.06	14.4±0.09	5.7±0.04
H10	30.3±0.36	35.8±0.17	20.1±0.13	10.5±0.09	3.3±0.04
A1	20.1±0.44	34.0±0.92	21.0±0.62	16.14±0.07	2.9±.03
A2	21.7±0.36	36.2±0.44	25.6±0.26	14.1±.09	2.3±0.06
A3	17.1±0.46	42.3±0.2	11.9±0.09	12.9±0.07	3.7±0.03
G3	23.6±0.61	37.0±0.17	23.2±0.15	11.3±0.08	2±0.21

The size distribution of all formulations indicated that the prepared formulations resulted in a reasonably small floating micro particulates (table 3).

Table 3: Cumulative percent undersize distributions of ranitidine HCl microparticulates prepared by melt granulation method (n=3) (average±SD)

Formula	<0.106 mm	<0.355 mm	<0.5 mm	<0.710 mm	<0.85 mm
H1	26.0±0.26	53.4±0.53	75.6±0.44	91.8±0.31	96.7±0.26
H2	27.1±0.17	54.3±0.2	76.1±0.17	91.4±0.18	97.4±0.22
H3	32.7±1.05	66.5±1.2	83.7±1.13	92.5±0.14	94.2±0.14
H4	25.6±0.3	58.7±0.25	75.9±0.28	90.2±0.24	94.2±0.15
H5	26.2±0.2	60.9±0.17	81.4±0.18	91.1±0.18	93.9±0.17
H6	29.1±0.26	61.5±0.26	82.9±0.16	94.2±0.15	97.9±0.16
H7	19.9±0.17	54.9±0.26	79±0.35	93.2±0.34	98.1±0.38
H8	24.7±0.26	56.3±0.2	80.3±0.26	94.4±0.24	97.4±.25
H9	21.4±0.4	53.5±0.05	76.4±0.11	90.8±0.02	96.5±0.03
H10	30.3±0.36	66.1±0.44	86.2±0.55	96.7±0.58	100.0±0.56
A1	20.1±0.44	54.1±0.61	75.1±0.78	91.2±0.75	94.1±0.76
A2	21.7±0.36	57.9±0.17	83.5±0.26	97.6±0.26	100.0±0.27
A3	17.1±0.46	59.4±0.56	71.3±.48	84.2±0.54	87.9±.53
G3	23.6±0.61	60.6±0.7	83.8±0.83	95.1±0.82	97.1±0.98

Flow properties

The flow properties of pure drug and samples of formulated floating micro particulates were evaluated by measuring the angle of repose, Hausner ratio and Carr's compressibility index as shown in table 4. Hausner ratios and Carr's compressibility indices ranged from 1.17 to 1.289 and 14.54 to 22.4%, respectively. The results are acceptable for granules and in agreement with previous studies [13]. It has been reported that material would be considered showing excellent flow properties when having an angle of repose equal to or less than 40˚. All formulations showed excellent flow ability as represented in terms of angle of repose (≤40°) [16]. Furthermore, it was obvious from the results in table 4 that all the prepared floating micro particulates had similarly bulk and tapped densities.

Table 4: Bulk density, tapped density and flow properties of ranitidine hydrochloride floating micro particulates samples prepared by method melt granulation in terms of angle of repose, Hausner's ratio and Carr's compressibility index of the prepared formulations, as compared with ranitidine hydrochloride powder (n=3) (average±SD)

Sample	Bulk density (g/ml)	Tapped density (g/ml)	Angle of repose (degree)	Hausner's ratio	Carr's index (%)
H1	0.43±0.01	0.51±0.02	34.88 °±1.31	1.188±0.02	15.85±1.52
H2	0.46±0.02	0.55±0.02	37.48 °±0.85	1.196±0.04	16.36±2.97
H3	0.43±0.01	0.54±0.01	36.57 °±0.44	1.256±0.05	20.37±2.92
H4	0.42±0.01	0.53±0.01	37.9 °±1.45	1.262±0.05	20.75±3.38
H5	0.42±0.03	0.53±0.01	34.59 °±1.64	1.262±0.06	20.75±4.03
H6	0.45±0.01	0.58±0.02	33.69 °±1.46	1.289±0.05	22.40±2.88
H7	0.44±0.02	0.53±0.01	29.7 °±1.04	1.205±0.03	16.98±2.09
H8	0.43±0.02	0.52±0.01	29.7 °±2.22	1.209±0.05	17.31±3.72
H9	0.46±0.01	0.55±0.01	32.83 °±1.42	1.196±0.02	16.36±1.68
H10	0.47±0.01	0.55±0.02	32.4 °±1.67	1.170±0.06	14.54±4.44
A1	0.39±0.01	0.47±0.01	38.42 °±1.2	1.205±0.06	17.02±3.9
A2	0.38±0.01	0.46±0.02	33.65 °±0.62	1.211±0.05	17.39±3.77
A3	0.39±0.02	0.47±0.01	36.13 °±1.88	1.205±0.06	17.02±4.13
G3	0.37±0.02	0.46±0.03	37.02 °±1.45	1.243±0.2	19.56±1.56
Ranitidine HCl	0.26±0.02	0.47±0.01	50.71 °±0.76	1.808±0.15	44.44±4.79

Content of ranitidine hydrochloride in the prepared floating micro particulates

The drug content of the various floating formulations was observed to be in the range 100±7%, which complies with the Pharmacopeial requirements [17].

***In vitro* release studies**

Ranitidine hydrochloride concentrations (mg/100 ml) over the whole dissolution rate study of the different formulations were plotted against time and the results are presented in fig. 1-5.

Incorporation of different types and percentages of Compritol® (A1, A2, A3) and hydrogenated castor oil (H1, H2 and H3) in the floating lipid matrix highly affected the release of ranitidine from the floating micro particulates. It could be observed from fig. 1 that floating micro particulates made of Compritol® (A1, A2, A3) showed a relatively higher release properties compared to those made of hydrogenated castor oil (H1, H2, H3). This finding is in accordance with previous studies, e. g. [1]. On the other hand, Zantac® tablets exhibited fast drug release amounting to 100% in about 30 min.

It was also observed that increasing the proportion of the fatty component (1:2, 1:2.5 and 1:3) was accompanied by proportional retardation in ranitidine HCl release. This behavior was encountered with both Compritol® and hydrogenated castor oil based floating RFM. Furthermore, it could be concluded that hydrogenated castor oil showed higher affinity to retard RH release, compared to Compritol®; however, the retardation in both fatty bases was a function of their proportions in the respective formulations (fig. 1).

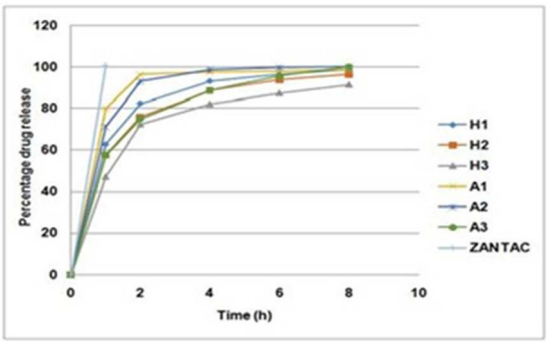


Fig. 1: *In vitro* release data of ranitidine HCl from floating micro particulates prepared using compritol® (A1, A2, A3) or hydrogenated castor oil (H1, H2, H3) in 0.1 N HCl (n=3) (average±SD)

The release effect of several additives incorporated in the prepared floating RFM, namely, ethylcellulose, PVP k90 and Aerosil® 200, was investigated. The results are illustrated in fig. 2-5.

Incorporation of Aerosil® 200 (hydrophilic colloidal silicon dioxide) in the floating micro particulates (H7, H9, H10) affected the release of ranitidine HCl only in early stage (1 and 2 h), as it could decrease burst release of the formulation (fig. 2). The decrease in release in the early time points could be due to the interaction of similar groups on the surface of different particles of colloidal silicon dioxide via chemical bonds with each other to form connecting bridges. This, in turn, leads to the immobilization of dissolution medium and gel layer formation which could reduce burst effect at early points. The relatively slight increase in dissolution afterward could be due to the disintegration effect of hydrophilic colloidal silicon dioxide [18].

The effect of ethyl cellulose as a release retarding agent is illustrated in fig. 3. Formulations containing ethyl cellulose (H4 and H5) showed a relatively slower drug release compared with the formulation devoid of ethyl cellulose (H3). The retardation is mainly observed starting from 2 h till 8 h following the initiation of the release study. Contrary to what was expected, the lower proportion of ethyl cellulose (H4) resulted in a relatively greater retarding effect compared with (H5) containing the higher proportion of ethyl cellulose (fig. 3). It could be suggested that increasing the proportion of ethyl cellulose (H5) may result in increasing the porosity of the prepared particles resulting in enhanced release compared with (H4) [11].

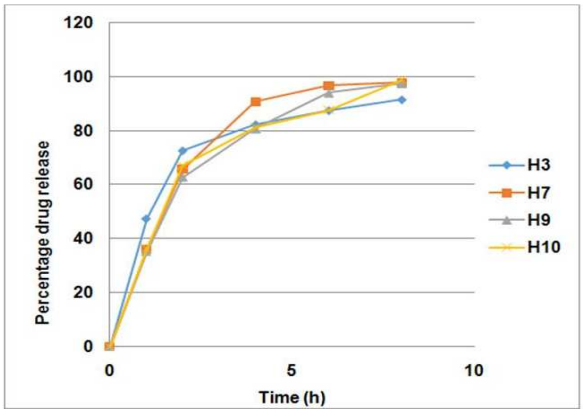


Fig. 2: *In vitro* release data of ranitidine HCl from floating microparticles prepared using hydrogenated castor oil with and without the Aerosil® 200 (H3, H7, H9, H10) in 0.1 N HCl (n=3) (average±SD)

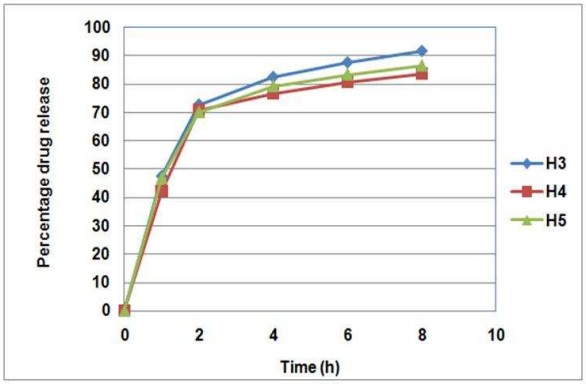


Fig. 3: *In vitro* release data of ranitidine HCl from floating micro particulates prepared using hydrogenated castor oil with and without the addition of ethylcellulose (H3, H4, H5) in 0.1 N HCl (n=3) (average±SD)

Fig. 4 shows the effect of PVP K90 on the release of ranitidine HCl from floating micro particulates prepared using hydrogenated castor oil (H6), pointing out a remarkable reduction in release pattern of the drug from the floating micro particulates. The combined effect of Aerosil® and PVP K90 as retarding agents is shown in fig. 5. H8 showed a relatively lower release of the drug compared to H3. However, no remarkable difference could be observed between the combined effect (H8) and the single effect of either Aerosil® alone (H4) or PVP alone (H6) (fig. 1-5).

Dissolution efficiency

The dissolution profiles were characterized by the calculated dissolution efficiency (DE%). The observed values range from 64.5-93.4%. The minimum drug release and consequently maximum retardation were observed with Cutina® HR (H6), whereas maximum drug release and minimum retardation were in the case of glyceryl monostearate formulation (G1).

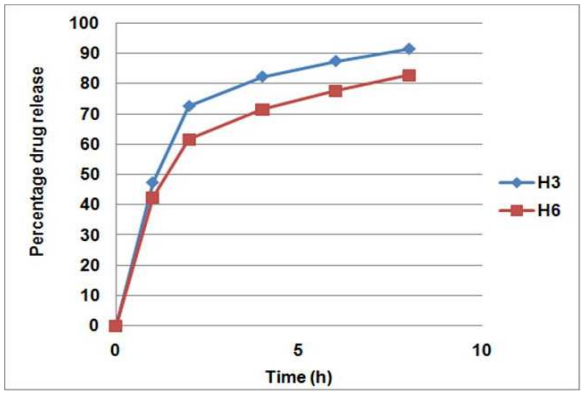


Fig. 4: *In vitro* release data of ranitidine HCl from floating micro particulates prepared using hydrogenated castor oil with and without the addition of PVP K90 (H3, H6) in 0.1 N HCl (n=3) (average±SD)

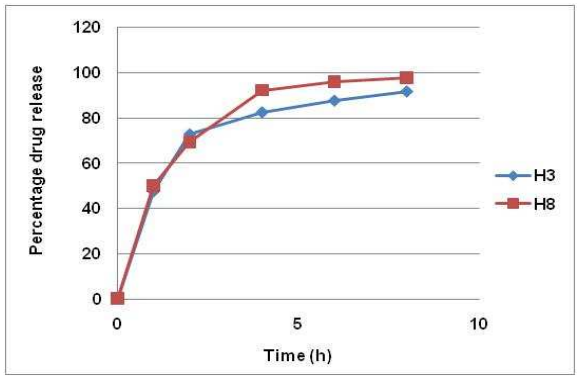


Fig. 5: *In vitro* release data of ranitidine HCl from floating micro particulates prepared using hydrogenated castor oil with and without the addition of PVP K90 and Aerosil® 200 combinations (H3, H8) in 0.1 N HCl (n=3) (average±SD)

***In vitro* buoyancy studies**

The floating capability of the prepared micro particulates was performed by the *in vitro* buoyancy studies. The floating lag time is the time taken by RH multi-particulates to appear to the surface of the dissolution medium. The micro-particulates floated immediately on the medium, and the floating lag time (min.) was zero for all the tested formulations. The percent of floating multi-particulates of different formulations after 12 h ranged between 75% (G1) and 99.9% (H7).

The absence of floating lag time is ideal to prevent dosage form from the transition to the intestine. The absence of lag time could be due to the low density of formulations. The percent of microparticulate floating at the end of buoyancy studies was almost 100% in all

formulations with the exception of formulations prepared using glyceryl monostearate (G1). The observed overall higher floating tendency (>98%) of the prepared formulations render them good candidates for further investigations [19].

Scanning electron microscope

The surface morphology of some selected formulations as examined by SEM is shown in fig. 6-8. Microparticulates exhibited in general pores of variable intensities. The surface of (H9) appears to show flakes that could be of silicon dioxide (Aerosil® 200).

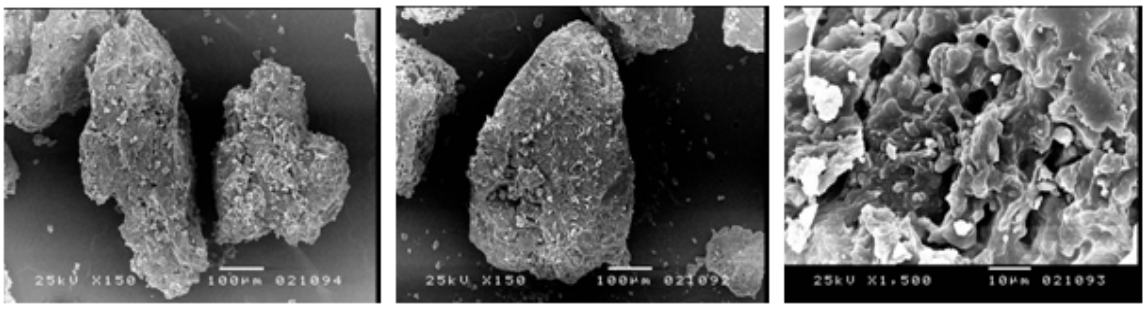


Fig. 6: Photographs showing surface morphology of ranitidine hydrochloride micro particulates (formula H5) in different magnifications

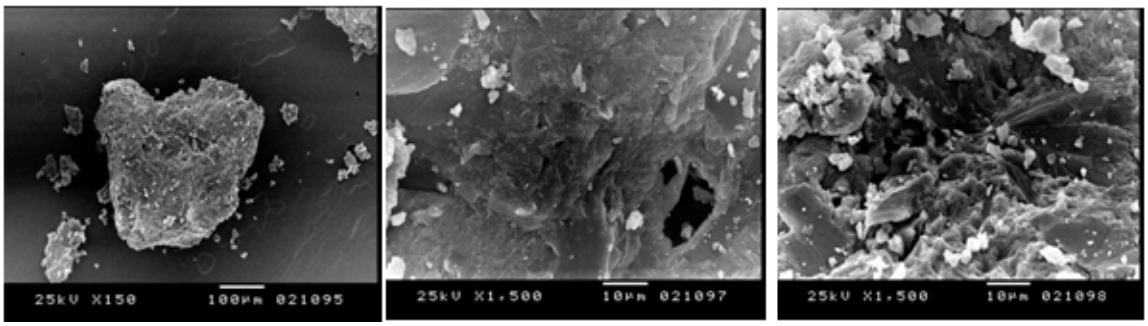


Fig. 7: Photographs showing surface morphology of ranitidine hydrochloride micro particulates (H6) in different magnifications

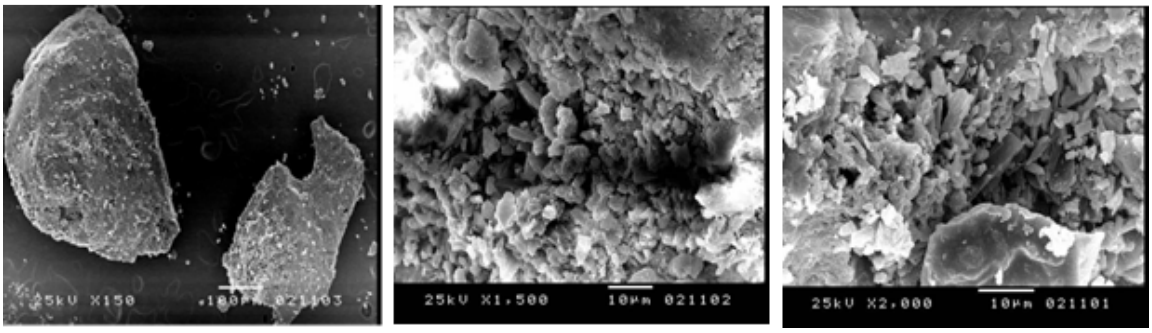
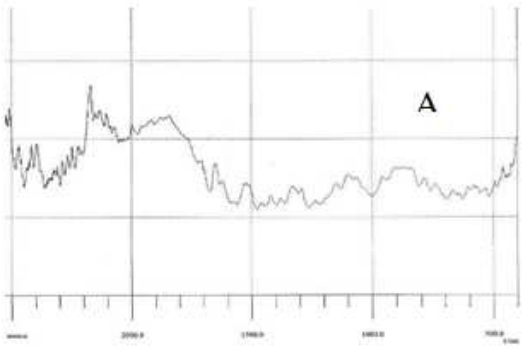


Fig. 8: Photographs showing surface morphology of ranitidine hydrochloride micro particulates (H9) in different magnifications

Fourier transformer infra-red spectroscopy (FTIR)

The infra-red spectra (fig. 9) of RH pointed out the characteristic peak at 2510 cm^{-1}(attributed to the N+and–H bond in protonated tertiary amine group), a prominent IR absorption band at 1620 cm^{-1} due to stretching vibration of C=N of amine group, and another characteristic peak of N=O at 1421.14 cm^{-1}.

The IR spectra (Data not shown) of Cutina® HR and all formulations proved the presence of a strong band at 1746 cm^{-1} related to C=O (ester) group. Furthermore, the spectra indicated that neither new IR absorption bands characteristic of complex formation nor disappearance of bands was observed. Besides, no shift or broadening of characteristic bands was observed, indicating the compatibility of the used excipients with the active ingredient [20].



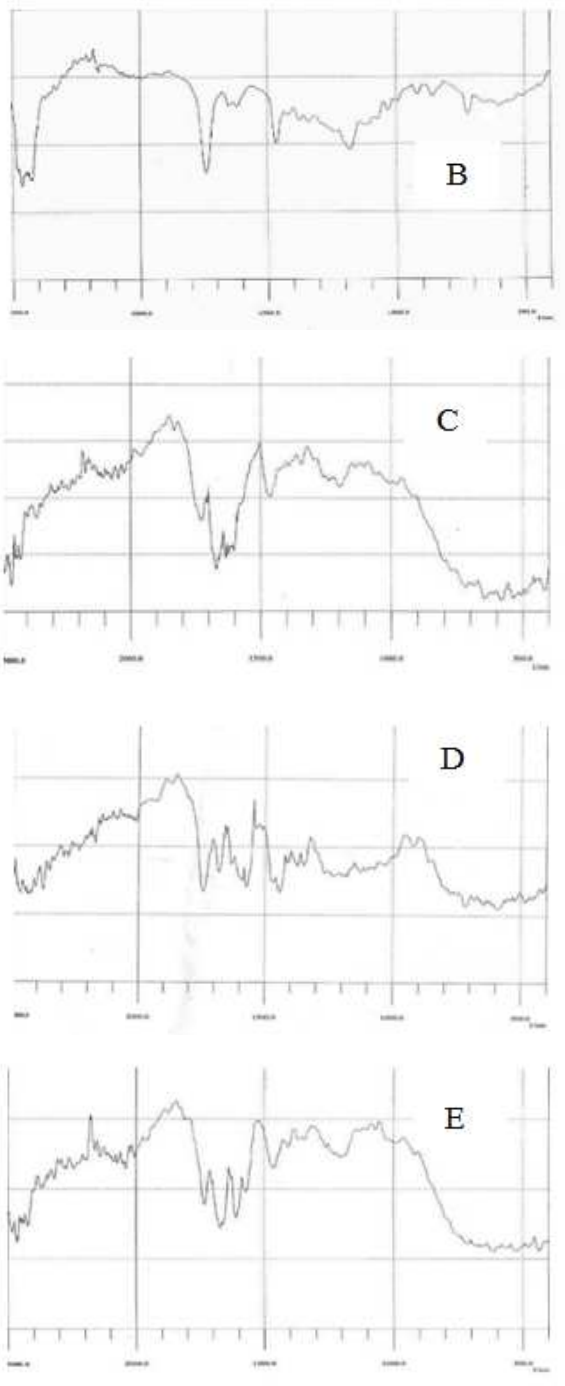
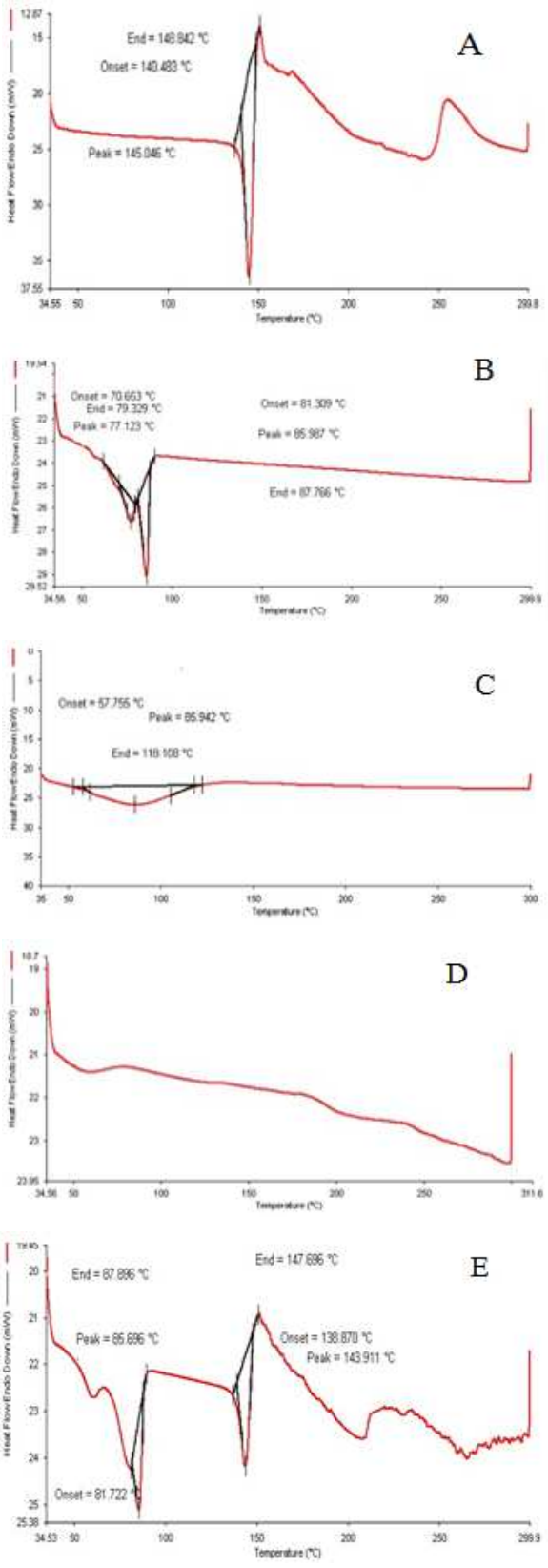


Fig. 9: The infra-red spectra of ranitidine hydrochloride (A), Cutina HR (B), H5 floating microparticulates (C), H6 floating microparticulates (D), and H9 floating microparticulates (E)

Differential scanning calorimetry (DSC)

DSC scans of the individual components and the RFM were performed (fig. 10). The results showed that RH exhibited a sharp endothermic peak at 145.05 °C, Cutina® HR showed an endotherm at 77.123 °C, and PVP K90 showed a broad endotherm at 85.9 °C while ethyl cellulose did not display any thermal event in the examined temperature range. The DSC curve of H5 microsphere showed the endothermic peak of the carrier around 85.7 °C and the endothermic peak of the drug at 143.9 °C. The DSC curve of H6 microsphere showed the endothermic peak of the carrier around 82.5 °C and the endothermic peak of the drug at 144.9 °C. The DSC curve of H7 microsphere showed the endothermic peak of the carrier around 86.1 °C and the endothermic peak of the drug at 146.16 °C. It could be concluded from the DSC results that there was no appreciable interaction between the drug and the other ingredients as indicated by the presence of the characteristic peaks of the pure drug and the individual additives almost in the same temperature range observed in the formulated micro particulates.



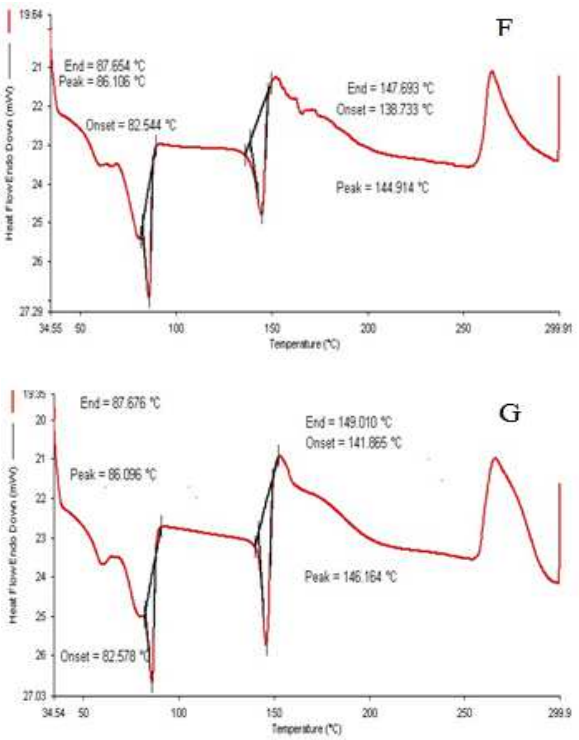


Fig. 10: Differential scanning calorimetry (DSC) thermograms of ranitidine hydrochloride (A), Cutina HR (B), PVP K90 (C), ethyl cellulose (D), ranitidine floating microparticulates H5 (E), ranitidine floating microparticulates H6, and ranitidine floating microparticulates H9 (G)

Stability studies

To assess the formulation stability, the accelerated stability studies were performed for 6 mo. The floating micro particulates of formulae H5, H6 and H9 were stored in 30 ml HDPE bottles properly capped and placed in an aluminum pouch. Stability studies were performed at 40±2 °C/75 % RH according to the ICH guidelines [21]. The stability studies in terms of floating time, assay and drug release were carried out and samples were examined after 0, 1, 3, and 6 mo. Formulations were evaluated for any physical or chemical changes after storage.

Only after 6 mo, there was a slight difference in the *in vitro* dissolution profiles, compared to zero time (fig. 11), an increase in DE% of H5 and H6 was observed. On the other hand, the dissolution efficiency of H9 was decreased (from 71.24 to 69.3) indicating slight drug release retardation in comparison with zero time. The observed DE% values after storage were 78.2, 73.7, and 69.3% for H5, H6, and H9 respectively. The corresponding values for the freshly prepared microparticles were 70.5, 64.6, and 71.24%. *In-vitro* drug release profile of ranitidine floating micro particulates after 6 mo at 40°C/75 %RH was compared with drug release profile of the same formulation at zero time. The data obtained from *in vitro* drug release was used to determine the similarity factor and dissimilarity factor between different formulations. The similarity factor (f2) and dissimilarity factor Q1 (f1) were calculated using the formulas (Shah *et al.*, 1998).

$$f_2 = 50\log\left\{\left[1+\frac{1}{n}\sum_{t=1}^{n}(R_t - T_t)^2\right]^{-0.5} x100\right\}$$

Where n is the number of time points, Rt and Tt are the dissolutions of the formulation at zero time and after 6 mo at 40°C/75 %RH, respectively. In general, f2 values higher than 50 (50-100) shows the similarity of the dissolution profiles of H5and H9 and dissimilarity of H6.

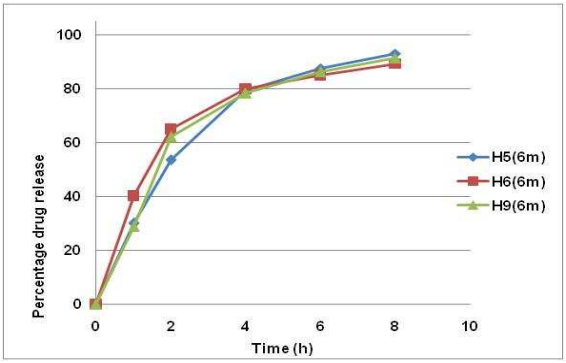


Fig. 11: *In vitro* release data of ranitidine HCl from floating micro particulates after 6 mo in accelerated stability study (H5, H6, H9) in 0.1 N HCl (n=3) (average±SD)

Drug content and %-floating

The recorded drug content values after 6 mo were 95.4, 93.8, and 92.8 for H5, H6, and H9; compared to 102.0, 107.4, and 99.8% at zero time, respectively. The corresponding values for %-floating were 95.5, 96.5, and 99.4; compared to 99.1, 99.8, and 99.6% at zero points, for H5, H6, and H9, respectively. The results revealed insignificant changes in microparticle properties over 6 mo.

CONCLUSION

1. The prepared microparticles exhibited optimum particle size (more than 90% of the prepared microparticles are less than 710 µm), good compressibility, and flow properties (angle of repose ≤40 °).

2. RFM containing Compritol® showed a relatively higher release properties compared to hydrogenated castor oil.

3. Increasing the proportion of the fatty component was accompanied by retardation in RH release.

4. The percent-floating of RFM was almost 100% in all formulations with the exception of formulations prepared using glyceryl monostearate.

5. FT-IR and DSC indicated the compatibility of the excipients with RH. Stability results revealed an insignificant change in RFM properties over 6 mo.

6. Stability studies of the selected formulation H5 and H9, at 40°C/75 %RH showed no significant changes in release profile (with f2 value at 6 mo of 54, 63, respectively taking zero time as reference). Furthermore, the main physical parameters, such as flowability, *in vitro* buoyancy, total drug content, and drug release, exhibited similar stability upon aging. H5 and H9 was stable for up to 6 mo at 40 °C/75% RH.

7. Although H6 exhibited good physical and chemical parameters at zero time but stability study showed significant changes in release profile after 6 mo at 40°C/75 %RH (with an f2 value of 49).

CONFLICTS OF INTERESTS

Declare none

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