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Optimization of ranitidine hydrochloride based on stability performance in directly compressible immediate and sustained release formulations

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Abstract: Ranitidine hydrochloride (RTD), a moisture-sensitive drug, has issues of stability during shelf life especially when formulated through wet granulation method. In current study, RTD was blended with non-hygroscopic excipient like ethyl cellulose and compressed using direct compression method. The physical and physicochemical characteristics were evaluated including hardness, thickness, diameter, friability, weight variation, disintegration, dissolution and accelerated stability study to optimize findings. Subsequently, the optimized formulation was characterized for Fourier Transform Infrared (FTIR) analysis and *in vitro* drug release kinetics. The physical characterization was unaffected by polymer variation while the friability and weight variation were within the USP limits. *In vitro* drug release depicted that the release rate was sustained by increasing the amount of ethyl cellulose, with a 10% increase of ethyl cellulose 99.09% drug was released. FTIR analysis exhibited no interaction among the ingredients of the optimized formulation (E2). The optimized formulation followed Hixson-Crowell release kinetics. Formulation A5 displayed immediate release characters as plain uncoated formulation. Accelerated studies showed no significant change in the drug content. The RTD was successfully sustained to be released up to 6 h and accelerated stability showed that the optimized formulation (E2) containing 4% starch 1500 and 10% of ethyl cellulose, respectively, was stable up to 6 months.

Keywords: Ranitidine HCl, stability, starch 1500, sustain release, ICH guidelines, avicel® PH102, stability studies

INTRODUCTION

Though various routes are available for the delivery of the drug into the body, the prime aspect regarding the production of the formulation requires that the integrity of the drug as well as the dosage form should be sustained. The processing factors, the ingredients as well as the real-time performance of the dosage form during the stability study or shelf-life should depict stable homing of the contents and orientation of the molecular structure of a drug (Ali and Ahmed, 2018). The instability of the drug can either be due to physicochemical properties, temperature or moisture sensitivity. The physicochemical instability of the drug enforces dosage form towards the formation of the tablet dosage form (Darji *et al.*, 2018). While moisture and temperature sensitivities represent the instability issues of a drug molecule and is a predictor that such agents should be carefully formulated during large-scale manufacturing of medicines (King *et al.*, 2020, Arshad *et al.*, 2021).

Nevertheless, it is a general perception that the drier is the dosage form, the more is the stable drug. Because the addition of moisture at any stage of manufacturing will result in the chances of deterioration of moisture-sensitive drugs (Bjerknes *et al.*, 2017). Subsequently, tablets not formulated through the wet method are considered to be the stable platform for moisture sensitive drugs (Pandi *et al.*, 2020).

The direct compression technique offers versatile advantages like time-saving, economical, non-laborious process of tablet manufacturing. It consumes less processing time, has limited labor costs and fewer process steps required (Lawal, 2019). So, theoretically, it is of utmost desirable to safely home drugs with thermal or moisture sensitivity. On the other side, the function of an excipient can be well-defined as the property of the material that helps and improves the function, appearance, taste, quality, performance and manufacturing of the drug product.

The stability of moisture-sensitive drug RTD was explored in a study where it was found that higher temperature during formulation processing may cause the production of toxic metabolites from the drug. So, it is very important not to involve processing conditions with a temperature higher than 50℃ (Abe *et al.*, 2020).

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Therefore, the aim of current research was to improve the stability of RTD formulated through direct compression using polymers like ethylcellulose, Avicel®, Aerosil®, mannitol and starch to produce immediate as well as sustained releases of drug. The dosage form was characterized for physical as well as physicochemical evaluation of the dosage form. The formulations were then optimized based on acceptable stability testing outcomes and complete drug release.

MATERIALS AND METHODS

Materials

Ranitidine hydrochloride (RTD) was kindly donated by Irza® Pharmaceutical Pvt. Ltd. (Pakistan). Other ingredients like mannitol, starch 1500 and Aerosil® 200 were provided by Schazoo Zaka® Pvt. Ltd (Pakistan), whereas ethylcellulose (EC) and Avicel® PH102 were gifted by Hoover Pharma (Pakistan). All other chemicals, reagents or solvents, wherever used, belonged to analytical grade. Double distilled water was used during the study unless otherwise prescribed.

Formulation technique

Different formulations, coded with A1-A5, AE1-AE5 and E1-E5, were formulated based on varying concentrations of Avicel®, starch, EC and Aerosil®. Briefly, ingredients were accurately weighed on analytical ATX124 (Shimadzu®) according to the specific quantities (Table 1). Then, the ingredients were mixed geometrically in the pestle and mortar for approximately 5 min in such a way that the diluent was added to the polymeric mixture. Then the formulation equivalent to the individual tablet weight was then shifted to a previously lubricated die cavity of a ZP-35 multi-punch rotary tablet machine for manual direct compression by using an 8 mm flat-faced punch and a compressing pressure of 3.5 tons for 5 s (Hanif *et al.*, 2021).

Physical evaluation of tablet formulations weight variation

Weight variation and standard deviation of all formulations were calculated to find the uniformity of weight per tablet. Tablets from each formulation code were subjected to a weight variation test for which an electronic weighing balance was used. Then average weight was calculated according to Equation 1 (Hussain *et al.*, 2016).

$$\text{Average } \boldsymbol{Weight} = \frac{\text{Total weight of 20 tablets}}{20} \quad \ldots \text{Eq. 1.}$$

Thickness and diameter

Both thickness and diameter of 20 tablets from each batch were measured using digital Vernier calipers with nil zero error and values were expressed as the mean of standard deviation for that respective formulation (Hanif *et al.*, 2017).

Hardness

Tablets were longitudinally placed in the jaw of a digital hardness tester to estimate the hardness of tablet formulations. Representative 10 tablets from each formulation code were selected for hardness estimation and results were expressed as a mean of standard deviation (Hanif *et al.*, 2022).

Friability

Roche® friabilator (MHK) was used to determine the percent tablet loss in terms of friability. Initially, tablet weight not less than 6.6 g from each formulation code was taken and placed in the friabilator (Hanif *et al.*, 2021). It was packed and rotated at 25 rpm for 4 min. After rotation, tablets were dedusted to remove any adhered torn particles and friability was calculated (Equation 2).

$$\text{Friabi}\boldsymbol{lity} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Final weight}} \times \mathbf{100} \quad \ldots \text{Eq. 2.}$$

Physicochemical evaluation of tablet formulations

Disintegration time (DT)

The United States Pharmacopeial (USP) disintegrating apparatus was used to determine the disintegration time of the formulated tablets. Briefly, 6 tablets from each batch of tablets were placed in the transparent tubes of the basket rack assembly. Temperature of the media was maintained at 37.5±0.5°C throughout the experiment. For sustained-release tablets, the disintegration time test was performed in two stages. Initially, the medium used was 0.1N hydrochloric acid (HCl), in the stage disintegration time test was performed for one hour. Latterly, the other medium used was phosphate buffer solution (PBS) adjusted to pH 6.8, test was performed, with discs placed on each tube, until tablets were completely disintegrated (Al-Gousous and Langguth, 2015).

In vitro drug release (DR)

The USP type II paddle dissolution apparatus (Agilent® 708-DS) was used to study the release profile of RTD. Regardless of the formulation code, the medium used for 2 h was 0.1N HCl, while afterwards, it was shifted to PBS adjusted to pH 6.8 (Razzaq *et al.*, 2021) for the next 4 h. Beakers of the dissolution apparatus was filled up to 900 mL and maintained at 37.5±0.5°C throughout the experiment and stirred at a rate of 50 rpm. Samples (5 mL) were withdrawn at defined time intervals up to 6 h. A fresh volume of media equivalent to the volume removed for sampling was added during each interval (Nigusse *et al.*, 2021).

Stability study

The stability of the compressed formulations was determined to estimate the concentration of RTD using accelerated stability study conditions which included 40± 2°C and relative humidity of 75%±5% (Hanif *et al.*, 2022).

Table 1: Percentage composition of immediate release (A1-A5) and sustained release (AE1-AE5, E1-E5) formulations

Code	EC	Starch	Avicel®	Aerosil®
A1	-	2	20	0.1
A2	-	2.5	25	0.1
A3	-	3	30	0.2
A4	-	3.5	35	0.3
A5	-	4	40	0.3
AE1	30	5	8	0.1
AE2	25	10	12	0.1
AE3	20	15	16	0.2
AE4	15	20	20	0.2
AE5	10	25	24	0.3
E1	5	2	-	0.1
E2	10	4	-	0.1
E3	20	6	-	0.2
E4	25	8	-	0.2
E5	30	10	-	0.3

Table 2: Physical characterization of the tablets formulated in the study

Code	Weight Variation mg ± SD	Thickness mm ± SD	Diameter mm ± SD	Hardness (kg/cm^2)	Friability (%)
A1	501.25 ± 1.45	3.35 ± 0.04	7.46 ± 0.02	9.12	0.38
A2	496.48 ± 1.89	3.36 ± 0.03	7.47 ± 0.03	10.53	0.31
A3	498.77 ± 2.31	3.34 ± 0.03	7.45 ± 0.02	9.87	0.29
A4	503.54 ± 0.24	3.37 ± 0.04	7.46 ± 0.01	11.23	0.22
A5	497.69 ± 1.45	3.35 ± 0.02	7.45 ± 0.02	11.69	0.18
AE1	498.59 ± 0.21	3.34 ± 0.04	7.46 ± 0.01	9.26	0.48
AE2	497.51 ± 2.14	3.36 ± 0.02	7.44 ± 0.03	8.93	0.41
AE3	496.85 ± 0.97	3.37 ± 0.03	7.45 ± 0.02	9.88	0.37
AE4	499.27 ± 0.21	3.35 ± 0.02	7.45 ± 0.02	10.47	0.29
AE5	500.78 ± 1.84	3.36 ± 0.01	7.47 ± 0.02	11.03	0.23
E1	496.63 ± 1.03	3.34 ± 0.04	7.44 ± 0.03	9.23	0.45
E2	500.26 ± 0.47	3.35 ± 0.03	7.46 ± 0.04	8.89	0.28
E3	498.51 ± 0.87	3.34 ± 0.02	7.47 ± 0.01	10.12	0.31
E4	497.25 ± 2.58	3.37 ± 0.03	7.46 ± 0.02	11.54	0.41
E5	498.64 ± 1.29	3.36 ± 0.03	7.45 ± 0.02	10.89	0.44

Table 3: Values of the r^2 and n for different release kinetic to evaluate the optimized dosage form.

Model	Coefficient r^2 (n)
Zero order	0.8140
First order	0.9714
Higuchi model	0.9265
Korsmeyer-Peppas model	0.9620 (0.643)
Hixson-Crowell model	0.9946

For accomplishment, tablets were blistered in double alu-alu foil and placed in the stability chamber under controlled conditions. In each interval, 10 tablets from the selected formulations were taken and crushed in a pestle and mortar. Then, the weight of powder equivalent to the single tablet was mixed in 900mL of PBS, in the case of sustained-release tablet, while 0.1N HCl was selected for immediate releasing formulations and stirred at 800rpm for 30 min. Then 5mL of the sample was collected and filtered to quantitate the results (Patel *et al.*, 2019).

Fourier transform infrared study (FTIR)

The FTIR analysis was performed on the powdered form of the pure drug, added ingredients and the physical mixture of the optimized formulation. Samples were run on Bruker Alpha™ (operated by OPUS) with Platinum-ATR in transmission mode at a scanning array of 4000-600 cm^{-1} (Hanif *et al.*, 2022).

In vitro release kinetics

Various mathematical models were applied to the *in vitro* drug release data of the optimized formulation to determine the mode of drug release from the tablet matrix. These models include zero order, first order, Higuchi, Korsmeyer-Peppas and Hixson-Crowell release models and the results were summarized (Hanif *et al.*, 2022).

Table 4: Outcome of the accelerated stability studies for the prepared formulations

Code	0 month		3 months		6 months	
	Physical Appearance	Assay (%)	Physical Appearance	Assay (%)	Physical Appearance	Assay (%)
A1	No change	98.65	No change	92.06	Very Slight change in color	86.92
A2	No change	97.43	No change	93.45	No change	89.81
A3	No change	98.65	No change	96.56	No change	91.67
A4	No change	96.83	Very slight change in color	90.18	Color slightly darkens	87.81
A5	No change	100.12	No change	91.45	Slight change in color	88.47
AE1	No change	99.41	No change	94.09	Color slightly darkens	87.73
AE2	No change	98.78	No change	92.54	No change	91.55
AE3	No change	100.04	No change	96.28	No change	90.65
AE4	No change	96.42	Very slight change in color	90.36	Slight change in color	85.94
AE5	No change	99.21	No change	94.32	Very slight change in color	90.76
E1	No change	97.63	No change	93.92	No change	89.54
E2	No change	100.07	No change	97.89	No change	95.65
E3	No change	97.51	No change	91.73	Slight change in color	85.42
E4	No change	98.23	No change	93.99	No change	90.67
E5	No change	97.71	Slight change in color	92.14	Color slightly darkens	88.04

STATISTICAL ANALYSIS

For the calculation of mean and standard deviation, the Microsoft® excel 2016 was used and results were calculated (Aqeela Raza *et al.*, 2021).

RESULTS

In an attempt to improve the stability of RTD, the formulations were compressed using direct compression method to avoid the incorporation of moisture and temperature (Dai *et al.*, 2019) as well as the ingredients under investigation were comparatively less hygroscopic (Kurakula and Rao, 2020) or agents that may be delivered with moisture-sensitive drugs like RTD (Etman *et al.*, 2016). Briefly, a force of 3.5 tons was used so that the flat-faced punch of the 500mg designated tablet should have a hardness in the range of 8-12Kg/cm^2. In the study, the higher concentration of Avicel® PH102 and pregelatinized starch (starch 1500) was added to evaluate whether the RTD release can sustain with the help of such ingredients as EC will be required for sustained release (Wasilewska and Winnicka, 2019).

Ethylcellulose possesses poor water-retaining properties, so, it was chosen to sustain the release of RTD. Similarly, starch was added as binder in different proportions (Ruszkay *et al.*, 2017). Mannitol was added to the formulation as diluent (Cheng *et al.*, 2020) since lactose has moisture-absorbing capabilities (Hebbink and Dickhoff, 2019). Mannitol was added to bulk the remaining weight of the tablet as it gains less moisture than lactose (Hanif *et al.*, 2017).

Physical characterization

The prepared tablets from each formulation code were evaluated for physical characterization and the results have been presented in table 2. Results revealed that the friability of the formulations was independent of the variation of the polymers as well as the quantities added were acceptable because the values were within the United States Pharmacopeia (USP) limit of less than 1%. The deviation of weight variation was also in accordance with the USP criteria of weight variation for tablets with an average weight of 500 mg i.e. 5%. Results showed that the SD of diameter and thickness was far less than 5% which confirmed that such values were unaffected by the changes in polymer quantity (Sarada *et al.*, 2017). The hardness was also in the range of preset criteria. The hardness was within the range of 8.89-11.69kg/cm$^{2.}$ For hardness, the maximum deviation was recorded for E1 which was 3.56. Between 496.48mg and 503.54mg, the average weight of all the formulations was observed. Maximum and least deviation was found for E2 and A1, which were 6.47 and 3.45% respectively. The lowest hardness was found with E2 while the highest was found with the formulation A5.

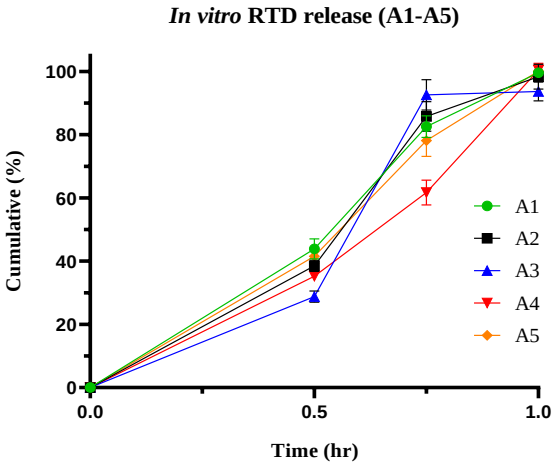

Fig. 1: *In vitro* RTD release from the formulations A1-A5

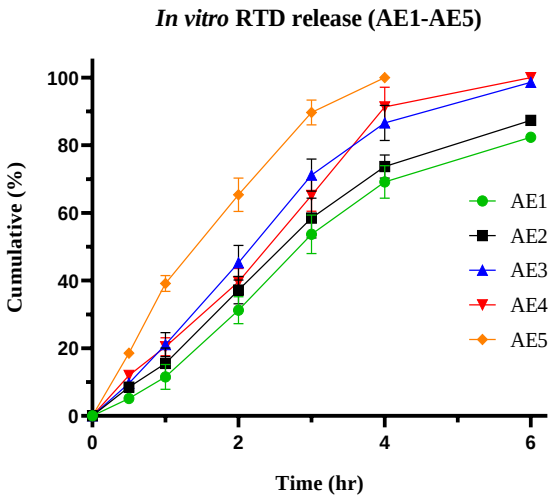

Fig. 2: Sustained release of RTD from formulations AE1-AE5

Disintegration test (DT)

The DT was performed on the formulations showing sustained release or release greater than 2 h from formulations as follows, which were, AE1-AE5 and E1-E5. The formulations were tested to withstand any abrasion or dismantling of ingredients of formulations for 2 h in 0.1N HCl media without disks. Results revealed that all the formulations passed the criteria for the disintegration testing procedure. When the tablets were immersed in the next phase in buffer 6.8 media with disks, all formulations except AE1 and E5 failed to disintegrate within 1 hour.

Formulations not containing EC i.e. A1-A5 were subsequently exposed to the testing criteria for plain uncoated tablets, which were less than 15 minutes with disks in 0.1N HCl. All formulations complied with the USP criteria for less than 15 minutes.

In vitro drug release

The *in vitro* drug release test was performed on all formulations. The preset criteria of release were up to 6 h was distinct or the sampling for the respective formulation was discontinued if the quantitative value was greater than 95%.

Results showed that all EC-containing formulations (AE1-AE5 and E1-E5) released the drug slower than the formulations containing avicel and starch alone (A1-A5), these formulations were unable to sustain and the complete drug was released (fig. 1) within 1 h (Yasmin *et al.*, 2020). While the formulations containing up to 10% of EC were able to sustain the release of the RTD till the 6 h and with a 5% concentration of EC, complete release of RTD was achieved at 4 h. Therefore, this value suggests that if the formulation is desired to release the drug for a longer period of time, then the amount of EC is required to be increased for sustain action. EC has a defined profile of sustain release (Zhu *et al.*, 2019).

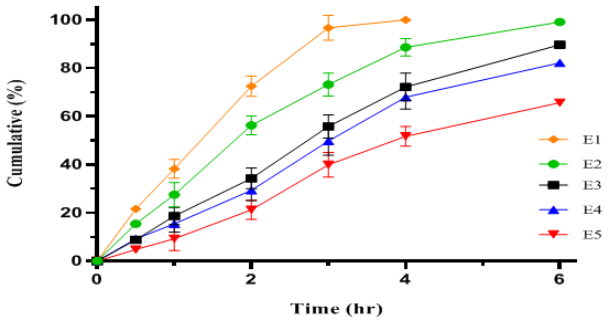

Fig. 3: The release of RTD from the formulations E1-E5

Formulations from AE1-AE5 depicted the faster release of the drug than E1- E5 (fig. 3) and slower release than A1-A5, which is linked with the concentration of EC. Sustain release behavior is linked with EC concentration, a sustained-release agent, which possibly retarded the release of water-soluble drugs (Gefter *et al.*, 2018). The slowest release was observed with AE1 containing the highest concentration of the EC and vice versa with AE5 (fig. 2). While the formulations AE3 and AE4 were able to sustain the release of RTD.

Accelerated stability studies

The accelerated studies were a short-term with more stressful conditions than long-term stability. It was assessed on the dosage form to evaluate whether the dosage form qualify the evaluation to safely home the moisture-sensitive drug. The stability conditions were applied to the conditions in which Pakistan was falling i.e. IVA (Khagga *et al.*, 2019). The USP monograph for Ranitidine HCl (RTD) states that the unit dosage compressed form must contain not less than 90% of RTD in the formulations and not more than 110% respectively. Results of the accelerated studies have been summarized in the following table 4. Results have shown that RTD was stable in all of the formulations as the contents of the RTD were not less than 90%. However, a very slight color change was observed on the surface of the table in formulations AE4, A4 and E5. The study on 6 months study revealed that the formulations A3, AE2, AE3, E2 and E4 were able to sustain the contents of RTD in the dosage form while most of the formulations had slight changes on the surface of the tablet. While out of A1-A5 formulations, formulation A3 complied with the complete release and passed the stability testing of RTD and depicted a value above 91% (table 4).

Formulations that passed the preset criteria of complete drug release till 6 h were AE3, AE4 and E2. Out of such, the stability of the formulation E2 was maximum which suggested that the capability of E2 was maximum in homing the contents of RTD safely in the maximum amount. So, E2 was optimized and studied for FTIR

analysis as well as *in vitro* release kinetics using DD solver®.

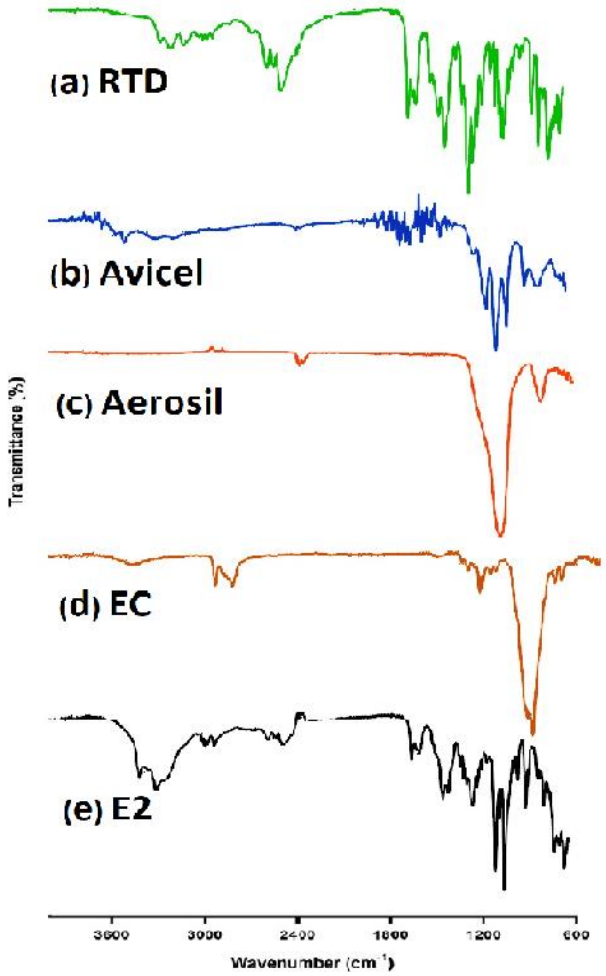

Fig. 4: FTIR spectra of the ingredients and the physical mixture in the optimized formulation.

Drug release kinetics

In vitro drug release kinetics was applied on the optimized formulation (E2) to estimate the mathematical model by which the drug was released from the matrix system of sustained released tablets. Various models were applied onto the release data of the E2. The model that has maximum value of r^2 was considered as the "best-fit" model. The values of all the model have been listed in the table 3. Maximum value of co-efficient was found with Hixson-Crowell model and the value was 0.9946. It referred that the release of the drug was dependent upon the constantly changing surface of the tablet when immersed in the dissolution fluid. The release was dependent upon the decay of the surface of the tablet (Ashraf Alhariri, 2020).

FTIR analysis

The FTIR spectra of the RTD, Avicel® PH102, Aerosil® 200 (fumed silica), starch and EC were compared with the peaks present in the literature. The spectral bands around 1621 and 1566cm^{-1} were due to the stretching of N–H bond. Similarly, absorption peak around 1609cm^{-1} was owing to the C-N bond in bending plane of its amino groups. For nitro functional group, a band peak was identified around 1240cm^{-1} (Wang *et al.*, 2020). In case of Avicel, the stretching of O-H bonding was depicted by small band absorption around 3330cm^{-1} which was in accordance with the findings (Putranti *et al.*, 2019). The EC spectrum depicted characteristic peaks of C-O-C stretching vibration around 1118cm^{-1} and absorption band in the range of 2852-2960cm^{-1}, depicting -CH3 stretching (Mohebian *et al.*, 2021).

The RTD peak exhibited no unusual or abnormal peak in FTIR of the optimized formulation was found which corresponds that no physical interaction was evident between the ingredients of the optimized formulation (fig. 4).

DISCUSSION

Moisture-sensitive drugs are prone to degradation during and after preparation for which numerous approaches have been implicated. However, in the current scenario, direct compression technique was employed. It was because the use of lesser hydrophilic can be an easy approach to safely load a drug in table form. To develop a stable drug formulation using lesser hydrophilic ingredients, the results of physical characterization complied with official compendial limits of USP. For achieving stability, Aerosil® 200 was added which has a profile of non-hygroscopicity (Zhang *et al.*, 2021). It also improves the release of drugs from directly compressible formulations (Ajayi and Amin, 2021). The insensitivity of fumed silica enhances the flowability of powder and granules by protecting them against humidity (Azad *et al.*, 2019). Likewise, in this study fumed silica was used for its non-hygroscopic properties to stabilize the moisture-sensitive RTD and also used as a glidant. Similarly, Avicel® PH102 was aided for compression because it has well-established binding properties and has been a choice of binder in direct compression technique (Chaerunisaa *et al.*, 2019). It is a widely used filler in direct compression technique because particles are held together by cohesive hydrogen bonding (Abu Fara *et al.*, 2020) and the position of hydrogen bond is adjacent to the cellulose molecules which gives them strength and cohesiveness, this also gives microcrystalline cellulose good binding property. This nature bonding also provides plasticity to the molecules during compaction (Sun and Sun, 2020). The appropriate percentage of microcrystalline cellulose to be used as binder and filler is 13 to 20%. The use of a lower percentage of microcrystalline cellulose leads to poor compression (Burke *et al.*, 2013). In the present study, Avicel was used in between 8 to 40%, but no wide difference was observed in the hardness and friability of

formulated tablets. Moreover, the disintegration of almost all formulations was achieved within time. Gelatinization of the starch results in the loss of its binding property due to which pregelatinized starch was aided for better compression (Azubuike *et al.*, 2019). Studies showed that improvement in dissolution profile as well as hardness and friability was achieved using pregelatinized starch. It is an excipient compatible with most pharmaceutical substances for which it is extensively used in pharmaceutical formulations worldwide.

Being hydrophobic, EC has been added in most of the formulations from matrix tablets, coated/uncoated pellets, microparticles and gels films for its sustained action property (Wasilewska and Winnicka, 2019). Moreover, the release of a drug from EC matrix tablets is dependent on the concentration of EC used in the formulation, the drug release rate decreases as the EC concentration increases (Borujeni *et al.*, 2020). The outcomes of *in vitro* drug release revealed that the increase in EC concentration in formulation produced a corresponding decrease in the drug release. EC has hydrophobic tendencies due to which when the concentration was augmented, it retained the drug in the formulation to a greater extent (Yang *et al.*, 2018). Accelerated stability studies were performed at 75% humidity for 6 months, which showed that formulations, A2, A3, AE2, AE3, E1, E2 and E4, remain stable because the USP requires that 90-110% of the RTD should be retained in the product (Irfan *et al.*, 2016). In the current study, the stability of RTD was noted in the range of 85.42-95.65% and optimization was performed on the basis of stability performance. The physical characterization was almost unaffected due to which the outcome of stability and complete drug release till 6 h was optimized. It was found that formulations with lesser degradation of RTD exhibited little or no change for the physical appearance of the formulation which is linked to the instability of the drug.

CONCLUSION

The formulations were designed to prepare directly compressible tablets using EC. Different formulations were prepared and evaluated for sustained-release of the drug up to 6 h. It was found that the physical characterization of the formulations was almost unaffected by changing polymer concentration. The formulations were tested for accelerated stability studies. It was concluded that the formulations containing 10% ethyl cellulose and 4% starch (E2) possessed the optimum drug release as well as Hixson-Crowell model-based drug release from the formulation. While AE4 was optimized for the immediate release of drug. While the formulation containing 30% Avicel® PH102 and 4% starch also exhibited stability for up to 6 months for the immediate release dosage form of Ranitidine HCl. Therefore, Ranitidine HCl was stabilized as sustained-release directly compressible matrix tablets. This study provides the platform for future studies, optimization of tablet characteristics manufactured by direct compression, using other moisture-sensitive drugs.

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