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DESIGN, DEVELOPMENT AND EVALUATION OF NOVEL ORAL MEDICATED JELLIES

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Abstract:

Ranitidine Hydrochloride has a very bitter taste. The bitter taste of the drug makes administration of the dosage form difficult, especially to paediatric patients. Oral medicated jellies are novel drug delivery systems overcoming these problems. They are sucrose based formulation thus providing higher compliance. These formulations are also advantageous for geriatric and dysphagic patents. Natural polymers used in jelly formulation are biodegradable, biocompatible, nontoxic, low cost and environment friendly, locally available, better patient tolerated and edible. The aim was to develop and evaluate oral jelly formulations of Ranitidine Hydrochloride. Preformulation studies, organoleptic, physical characteristics, drug content, pH, syneresis, taste masking and in vitro dissolution testing were conducted. The Fourier transform infrared and differential scanning calorimeter studies showed that there was no interaction between drug and excipients. The concentration of gelling agents influenced the spreadability. The formulation F4 showing good pourabilty and gelling property so it was selected for further optimization by varying the degrees brix (°Brix). The pH of all the formulations was found between pH 5 to 6. The optimized formulations (F4.3) masked the bitter taste of Ranitidine Hydrochloride and demonstrated acceptable physical properties with 50% drug release in 15 min. The formulation was tested for microbial growth and was found to be stable.

Key words: *Pediatrics, bitter taste, oral medicated jellies, natural polymers, ranitidine hydrochloride*

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INTRODUCTION:

Peptic ulcers may be defined as discontinuities of the gastric or duodenal mucosa with penetration to the muscularis mucosae and exposure of the submucosa [1]. The integrity of the upper gastrointestinal tract is balanced between "hostile" factors such as gastric acid, H. pylori, NSAIDs and pepsin, and "protective" factors such as mucus, bicarbonate, prostaglandins and blood flow to mucosa affecting gastrointestinal mucosa. Imbalance in these factors affects the gastric mucosa giving rise conditions like peptic ulcer [2]. There are a number of factors which lead to ulcer formation. Secondary ulcers, on the contrary, are caused by extragastric pathogenic events, like, stress or drugs. Cushing ulcers are associated with a brain tumor or injury. Ulcers also develop as secondary conditions to various diseases. Hypersecretory states like multiple endocrine neoplasia type I (MEN-I), antral G-cell hyperplasia, systemic mastocytosis, gastrinoma (Zollinger-Ellison syndrome), basophilic leukemias, cystic fibrosis, short bowel syndrome, and hyperparathyroidism may also lead to ulcerogenic state. Among all the causes use of use NSAID's and H.pylori are the most prevalent [3].

NSAID's reduce the hydrophobicity of gastric mucus this causes injury to surface epithelium by endogenous gastric acid and pepsin secreted. They inhibit cyclo- oxygenase -1 and cyclo- oxygenase -2. The anti-inflammatory properties of NSAIDs are mediated through inhibition of cyclo-oxgenase-2, and adverse effects of NSAID's such as gastric and duodenal ulceration, occur mainly due effects on the constitutively expressed cyclo-oxygenase-1 [4,5]. The *H. pylori* infected individuals have increased resting and meal-stimulated gastrin levels and decreased gastric mucus production and duodenal mucosal bicarbonate secretion, all of which favor ulcer formation [6,7].

Treatment of peptic ulcers includes use of antacids; H2 antagonist and proton pump inhibitors. H2 antagonist. H2 antagonist [8, 9]. Ranitidine Hydrochloride is a histamine H2-receptor antagonist. It is widely prescribed in various conditions like gastric ulcers, duodenal ulcers, Zollinger-Ellison syndrome and gastroesophageal reflux disease [10]. Ranitidine HCl acts as competitive inhibitors of histamine at the parietal cell H2 receptor. It suppresses the normal secretion of acid by parietal cells and the meal-stimulated secretion of acid [11].

Ranitidine has a very bitter taste which makes administration of its formulation non-compliant, especially to paediatric patients. Oral medicated jellies are novel drug delivery systems overcoming these problems [12]. They are sucrose based formulation thus providing higher compliance. These formulations are also advantageous for geriatric and dysphagic patents. Natural polymers used in jelly formulation are biodegradable, biocompatible, nontoxic, low cost and environment friendly, locally available, better patient tolerated and edible [13]. Taste masking of Ranitidine HCl is mainly by addition of sweeteners and flavours and entrapment of the drug in the gelling matrix[14]. Hence the present study was directed towards formulating oral medicated jellies for Ranitidine HCl using pectin as the polymer.

MATERIAL AND METHODS:

Ranitidine was gift sample from Orchev Pharma, Gujrat. Pectin was obtained from Brenntag, India. Citric acid, Tri sodium citrate and sodium benzoate were purchased from Vikas Pharma, Mumbai. Dextrose and sucrose were purchased from Loba Chemie. Mango flavor was obtained from Ultra International Pvt Ltd. All other chemicals were of analytical grade.

Preformulation studies

The preformulation studies were carried out for API Ranitidine HCl. Visual examination of Ranitidne HCl powder was carried out by transferring 50 mg on to white paper, spreading and examining visually in any light. Melting point was determined using capillary melting point apparatus. The solubility was determined by the equilibrium solubility method**.** An excess of the drug was placed in a solvent system and shaken at a constant temperature (30°C ± 2°C) over a period until equilibrium was obtained. In the present study, the solubility of Ranitidine HCl was tested in distilled water, phosphate buffers pH 6.8 and 0.1 N HCl at 30°C ± 0.2°C.

Drug – Excipient compatibility:

The drug excipient compatibility studies were conducted by analyzing FTIR spectra of pure Ranitidine HCl, a combination of Ranitidine HCl with excipients and blend of excipients kept in vials for periods of 4 weeks viz., 25° C ± 2° C/ 60% RH ±5% RH, accelerated stability storage conditions (40°C ± 2°C / 75% RH ± 5% RH)and 55°C ± 2°C.

The samples were analysed after 30 days. Fourier transforms infrared (FTIR) spectra (4000‑400 $cm^{-1}$and resolution of 4 cm^{-1}) of all the samples was measured by preparing dispersion in dry KBr using attenuated total reflectance FTIR spectrophotometer. The absorption maxima in the spectra obtained were compared, and the presence of additional peaks corresponding to the functional groups was noted.

DSC Studies:

The heat characteristics of CBZ and drug‑polymer mixtures were analysed using a Shimadzu®

Differential scanning calorimeter (DSC)-60 (Shimadzu, Kyoto, Japan). The behavior was studied by heating the samples (2 mg) from 25°C to 400°C at a heating rate of 10°C/min under nitrogen flow at 10 cm^3/min^{-1} using an empty aluminum pan as a point of reference.

Preparation oral medicated jellies:

For batches F1 to F3: Accurately weighed pectin (SS121) and trisodium citrate were mixed with 10% sucrose (taken from the total amount) and stirred into the water until the pectin is completely dissolved. Sucrose was triturated with the drug and was dispersed in dextrose syrup. This was added in the polymer solution. The mixture was stirred using an overhead stirrer (Remi Motors; type-RO122). The solution was heated till it reaches the desired brix. The brix was measured using handheld refractometer (Erma Inc.; Japan). Sodium benzoate was also dissolved in minimal quantity of water and added followed by mango flavour under continuous stirring. Citric acid solution was added to this under continuous stirring at 60°C to adjust the pH to 3.7 using pH meter (EcoTestr pH 2 Waterproof Pocket Tester). These batches were then subjected to drying.

For batches F4 and F5: Accurately weighed polymer powder pectin was mixed with 10% sucrose was dispersed in purified water containing of citric acid and trisodium citrate. Sucrose was triturated with the drug and was dispersed in dextrose syrup. The temperature was maintained at 60°C throughout preparation for both the mixtures. The dispersion was stirred using an overhead stirrer (Remi Motors; type-RO122) for 20 min to facilitate hydration of gelling agent. Then syrup mix was added to the polymer solution. The solution was heated till it reaches the desired brix or the total solid content. The brix was measured using handheld refractometer (Erma Inc.; Japan).Sodium benzoate was also dissolved in minimal quantity of water and added followed by mango flavour under continuous stirring. Citric acid solution was added to this under continuous stirring at 60°C to adjust the pH to 3.7. These batches were subjected to variable brix and drying time.

Evaluations of Oral medicated jellies:

Pourability of the mixture:

The jelly formulation mixture should be easily pourable in the moulds. The buffer salts (retarders) like trisodium citrate play an important role in this process.With the addition of these retarders the approaching of the pectin molecules during the hot phase is interfered sterically. They also raise the pH-value before the acid addition, thus preventing pre-gelation. The higher the buffer salt, i.e. retarder, concentration, the lower the setting temperature and the longer the setting time. This provides sufficient time for pouring and setting of the jelly.

Physical appearance:

Consistency and structure together make up the so-called texture. Texture is the overall impression of the sensory feeling and describes especially the mouth feel of a product. The texture of the prepared medicated jellies was analysed visually.

Stickiness and grittiness:

Texture of the medicated jelly in terms of stickiness and grittiness had been evaluated by visual inspection of the product after mildly rubbing the jelly sample between two fingers.

pH determination:

The pH value of 5-6 is considered optimal for gelling and taste reason. The pH of prepared jellies was measured using a digital pH meter at room temperature (25°C ± 5°C). For this purpose, 0.5 g of jelly was dispersed in 50 mL of distilled water to make a 1% solution, and the pH was noted.

Table 1: Fomualtion batches of Ranitidine Hydrochloride Oral medicated jellies.

Ingredients (in %)	F1	F2	F3	F4	F5
Ranitidine HCl	1	1	1	1	1
Pectin	1.3	1.5	4	2.2	2.5
Trisodium citrate	3.3	3.3	2	0.4	0.4
Citric acid	-	-	-	0.37	0.37
Sucrose	50	50	36	30	30
Glucose syrup	30	30	47.5	52	52
Citric acid solution 50%	1 ml	1.2 ml	1.4ml	0.8ml	1ml
Sodium benzoate	0.01	0.01	0.01	0.01	0.01
Water	22	22	20	30	30
Flavour	1ml	1ml	1ml	1ml	1ml

In vitro Taste analysis:
5 mL of pH 6.8 phosphate buffer (to simulate salivary pH and volume) was used to study the taste masking efficiency of jelly preparation. One jelly from optimised batch was placed in 50 mL beaker. 5 ml of the buffer solution was then added and the beaker was allowed to stand for 60 sec and 120 sec, respectively. After the specified time, the buffer solution was filtered. The filtrates were analyzed for drug content by UV. The test was performed in triplicate

Syneresis:
Syneresis is the contraction of the gel upon storage and separation of water from the gel. It is more pronounced in the gels, where lower concentration of gelling agent is employed. It is one of the major problems associated with low acylated guar gum gels [24]. All the jellies were observed for signs of syneresis at room temp (25°C ± 5°C) and 8°C ± 1°C.The formulations showing signs of syneresis were rejected and not considered for further studies.

Percent drug content:
Ranitidine HCl jellies were tested for their drug content. Twenty jellies were finely crushed to gel consistency; quantity of the gel equivalent to 50mg of Ranitidine HCl was accurately weighed and transferred to a 50ml volumetric flask. To the flask water was added and contents were mixed thoroughly and sonicated for 45minutes. The solution was made upto 50ml and filtered. Various dilutions of the solution were performed. The absorbance of the resulting solution was measured at 310nm using Shimadzu UV visible spectroscopy.

Dissolution studies:
The *invitro* dissolution study was performed by using a USP type 2 paddle apparatus at a rotational speed of 50rpm. 900ml of media was used as the dissolution medium and the temperature was maintained at 37° C± 0.5°C. A 5ml aliquot was withdrawn from the dissolution apparatus at specified time intervals for one hour and the same volume was replaced with the fresh dissolution media. The samples were filtered through whatman filter paper. Absorbance of these solutions was measured at 310nm in water by using Shimadzu UV visible spectroscopy. The drug release profile was calculated.

Microbial studies:
It is important to determine the microbial profile of jellies as they are contain pectin which is of natural origin and water which favors microbial growth. Microbial growth occurs due to improper maintenance and manufacturing conditions. The jellies were tested for E. coli, S. aureus and P. aeruginosa by culturing on pathogen specific mediums.

Requirements:
The working area for conducting microbial experiments viz. Laminar air flow chamber was sterilized by first cleaning the working platform and side frame with 75% isopropyl alcohol (IPA), followed by UV treatment for 20- 25minutes and then blower was kept on for the next 10-15 minutes.
All the glass apparatus used for conducting microbial experiments were sterilized in the autoclave (condition 121°Cand 15psi for 15minutes) followed by UV treatment for 20-25 minutes. The agar mediums and nutrient broth mediums used in these experiments were sterilized in autoclave (121°C and 15psi for 15minutes).
Preparation of sample stock solution:
1g jelly formulation was dissolved in saline solution and the volume was made up to 10ml with the saline solution.

Test for E.coli using Mac Conkey agar:
25ml of hot melted Mac Conkey agar medium was first poured in the sample and control petriplates and the medium was allowed to solidify in LAF chamber. After medium solidification, two nichrome loopful of stock solution of formulation was streaked in three sample petriplates.
Control petriplates:
Media control: 25ml of Mac Conkey agar medium was transferred in a petriplate.
Diluent control: 25ml of Mac Conkey agar medium was transferred in a petriplate and allowed to solidify. Two nichrome loopful of saline solution (diluents) was den streaked on the medium.
Positive control: 25ml of Mac Conkey agar medium was transferred in a petriplate and allowed to solidify. Two nichrome loopful of E. coli was streaked on the medium.
Test for S.aureus:
25ml of hot melted Vogel Johnson agar medium was first poured in the sample and control petriplates and the medium was allowed to solidify in LAF chamber. After medium solidification, two nichrome loopful of stock solution of formulation was streaked in three sample petriplates.
Control petriplates:
Media control: 25ml of Vogel Johnson agar medium was transferred in a petriplate.
Diluent control: 25ml of Vogel Johnson agar medium was transferred in a petriplate and allowed to solidify. Two nichrome loopful of saline solution (diluents) was den streaked on the medium.
Positive control: 25ml of Vogel Johnson agar medium was transferred in a petriplate and allowed to

solidify. Two nichrome loopful of S. aureus was streaked on the medium.

Test for P. aeruginosa:

25ml of hot melted Cetrimide agar medium was first poured in the sample and control petriplates and the medium was allowed to solidify in LAF chamber. After medium solidification, two nichrome loopful of stock solution of formulation was streaked in three **sample petriplates.**

Control petriplates:

Media control: 25ml of Cetrimide agar medium was transferred in a petriplate.

Diluent control: 25ml of Cetrimide agar medium was transferred in a petriplate and allowed to solidify. Two nichrome loopful of saline solution (diluents) was den streaked on the medium.

Positive control: 25ml of Cetrimide agar medium was transferred in a petriplate and allowed to solidify. Two nichrome loopful of P. aeruginosa was streaked on the medium.

RESULTS AND DISCUSSION:

Standardisation of drug

5.1.1 Appearance and melting point: The table 5.1 shows the results for appearance or standardization of drug

Table 2: Appearance and melting point

Sr No	Parameter	Results
1	Appearance	Creamish white
2	Melting point	142°C ±2°C

Solubility Studies:

The table 5.2 shows the results for solubility studies in 0.1 N HCl, water and 6.8 pH phosphate buffer

Table 3: Results of solubility studies

Sr no	solvent	Solubility
1	0.1N HCl	Soluble
2	Water	Freely soluble
3	pH 6.8 buffer	Soluble

Drug- excipient compatibility:

Physical examination of individual drug-excipient mixtures stored at 40°C and 75% RH was carried out for 45 days. The initial color of the drug-excipient mixtures observed as white to brownish for pectin and all other excipients along with the drug showed white to off white color. No characteristic changes were observed in color or physical state for all the samples at 15, 30 and 45 days. Fourier transforms infrared spectra of the pure drug is shown in Figure 1. Characteristic peaks of pure Ranitidine Hydrochloride are given in table no 4. The peaks were in compliance to those of standard values. No additional peaks corresponding to functional groups were obtained. There were no significant deviations found between the peaks of drug and those of drug-excipient mixtures that indicated the stability of the drug in the presence of all excipients. The FTIR spectra of Ranitidine HCl is shown in Figure 1

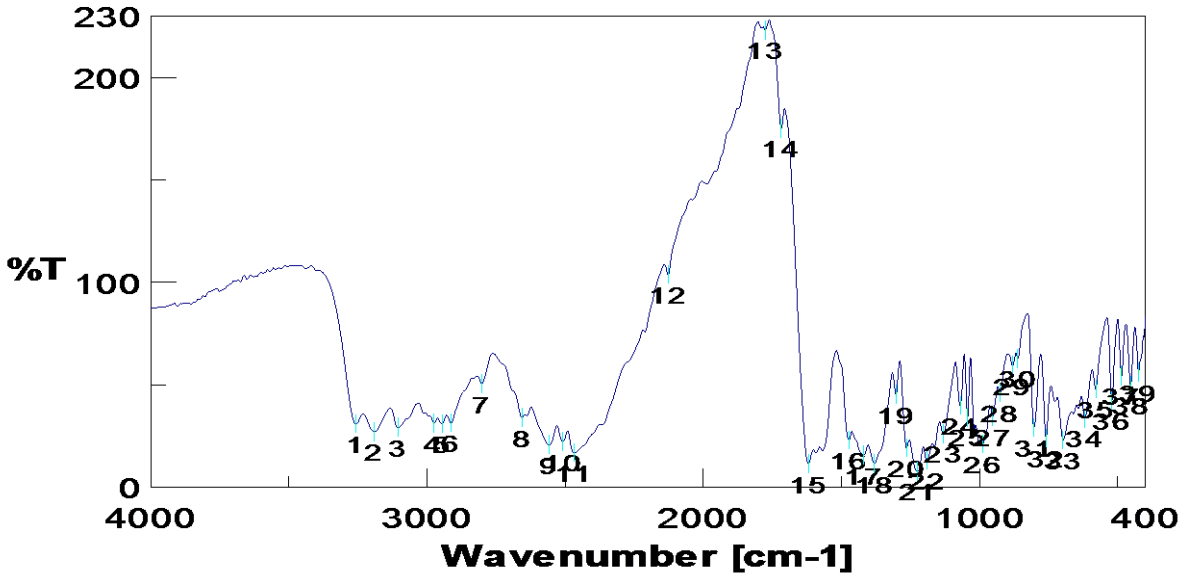

Fig 1: FTIR spectra of Ranitidine HCl

Table 4: Wavelength and corresponding functional groups in FTIR spectra of Ranitidine HCl

Wavelength	Functional group
2500cm^{-1}	N-H (in protonated tertiary amine)
1610 cm^{-1}	C=N stretching
1460 cm^{-1}	C-N

DSC Studies:

The DSC thermogram of pure drug demonstrated a sharp endothermic peak at 146.43°C corresponding to the melting point of the crystalline form of Ranitidine Hydrochloride. Whereas the thermograms of the mixtures of the drug using gelling agents and other excipients showed varying deviations in the characteristic peaks between 130°C and 150°C . This shifting of endothermic peaks to lower temperatures could be due to the formation partial drug-polymer complexes. The DSC thermogram of pure drug is shown in figure no. 2.

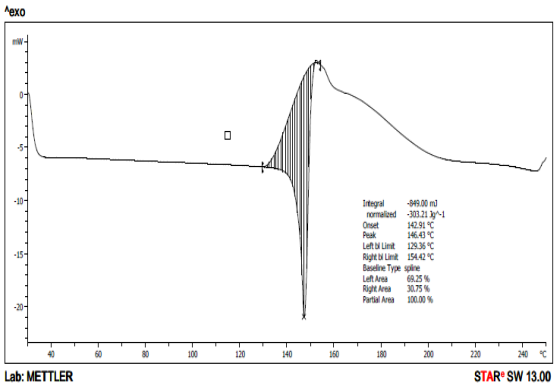

Fig 2: DSC thermogram of Ranitidine HCl

Selection of optimized formulation

Among the batches prepared batch F4 showed good pourability of mixture and gelling. The jelly formed had a firm and smooth texture. Hence this batch was selected as the optimized batch for further evaluation. The brix of the jelly was varied between 70– 80. Six batches were prepared with the following ^{o}brix.

Table 5: Optimisation of Batch F4 at different ^{o}brix values

Batch	^{o}Brix
F4.1	70
F4.2	72
F4.3	74
F4.4	76
F4.5	78
F4.6	80

Physical appearance:

The texture of the jellies prepared looked smooth and soft in appearance at brix 74°. At brix 80° the texture looked rough. Results of physical appearance are given in table no 7.

Stickiness:

All the jellies prepared showed stickiness. Hence the jellies were dried for 7hrs at 50^{o}C. The stickiness was found to be reduced after drying. Results of stickiness before and after drying are given in table no 7.

Table 6: Results of stickiness before and after drying

Batch	**Before drying**	**After drying**
F4.1	Very sticky	Sticky
F4.2	Sticky	Sticky
F4.3	Sticky	Less sticky
F4.4	Sticky	Less sticky
F4.5	Sticky	Less sticky
F4.6	Sticky	Sticky

pH of jellies :

The pH of the jellies of the optimized batch was found out to be between the optimum range of 4.9-6.3. Results of pH of jellies are given in table no 7.

Syneresis:

There was no syneresis observed in the optimized batch at the specified temperature.

***Invitro* taste analysis:**

There was no significant drug release observed during in vitro taste evaluation hence it can be correlated to taste feel. As insignificant drug was released, it is insufficient to impart bitterness.

Table 7: Results of physical appearance, pH and *invitro* taste analysis.

Batch	**Physical appearance**	**pH**	**% drug content (invitro taste analysis)**
F4.1	Very soft	5.89	3.40
F4.2	Smooth and very soft	5.74	1.34
F4.3	Smooth and firm	5.01	1.12
F4.4	Smooth	6.02	1.52
F4.5	Smooth	5.53	3.35
F4.6	Slightly rough	4.95	1.85

Dissolution study:

All the formulations of prepared oral medicated jellies were subjected to *invitro* release studies using dissolution apparatus in water. The release data obtained for all the formulations are tabulated in table no and figure no shows plot of percent drug released as a function of time for different formulations

Table 8: *Invitro* dissolution profile of Ranitidine HCl in water

Time intervals (mins)	F4.1	F4.2	F4.3	F4.4	F4.5	F4.6
5	35.71	40.71	43.77	34.58	39.17	48.75
10	50.45	62.76	62.01	64.26	56.63	62.81
20	70.16	74.60	70.40	77.25	66.90	73.88
30	73.56	81.52	74.62	83.42	73.39	76.20
45	78.08	85.80	87.77	84.27	79.16	79.30
60	80.50	87.80	92.20	90.47	87.63	84.71

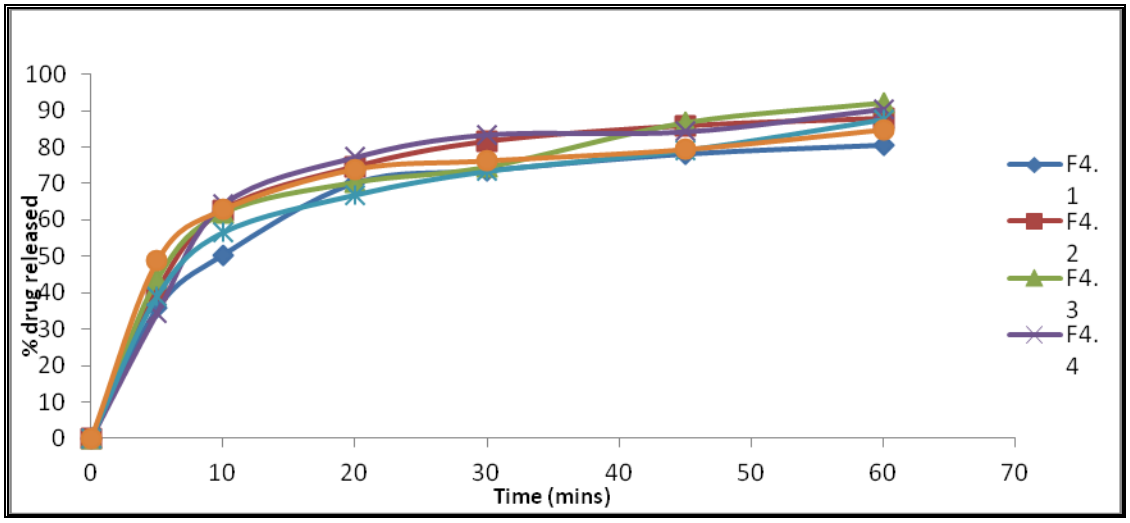

Fig 3: *Invitro* dissolution profile of Ranitidine HCl

Drug content:
The drug content of the formulation F4.3 was found to be 92.75% .

Microbial studies
Test for E.coli on Mac Conkey agar:

Table 9: Observed E. coli colonies in sample and control petriplates of formulation.

Microbes	No of E. coli colonies observed in sample pertiplates		No of E. coli colonies observed in Control pertiplates		
	i	ii	Medium control	Negative control	Positive control
F4.3	0	0	-	-	+

Test for S. aureus on Vogel Johnsons agar:

Table 10: Observed S. aureus colonies in sample and control petriplates of formulation.

Microbes	No of S. aureus colonies observed in sample pertiplates		No of E. coli colonies observed in Control pertiplates		
	i	ii	Medium control	Negative control	Positive control
F4.3	0	0	-	-	+

Test for P. aeruginosa on Cetrimide agar:

Table 11: Observed P. aeruginosa colonies in sample and control petriplates of formulation.

Microbes	**No of P. aeruginosa colonies observed in sample pertiplates**		**No of E. coli colonies observed in Control pertiplates**		
	i	ii	Medium control	Negative control	Positive control
F4.3	0	0	-	-	+

CONCLUSION:

In the present work oral medicated jellies of Ranitidine HCl were formulated by matrix entrapment technique and addition of sweeteners and flavors. The preformulation studies of solubility showed that Ranitidine HCl was freely soluble in water, pH 6.8 phosphate buffer and 0.1N HCl. DSC and FTIR studies showed that there was no apparent interaction between the excipients and the drug. Formulation batches prepared were checked for gelling and texture. Batch F4 was selected for further optimization by varying total solid content (brix) in the jelly formulation. All the batches showed pH between 4- 6. The optimized batch showed good texture with more than 50% drug release in 15mins. The *invitro* taste analysis was carried out which showed minimal amount of drug was released in simulated saliva proving that the bitter taste of the drug would not be sensed by the taste buds in the mouth. The dosage form prepared did not show syneresis at room temperature. Hence we conclude that a novel taste masking formulation of Ranitidine HCl has been developed for pediatric, geriatric and dysphagic patients.

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