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Design and evaluate the mebendazole taste mask chewable tablets using ion exchange resin Kyron T-114

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***Abstract*---**The aim of this research was to mask the bitter taste of Mebendazole using ion exchange resin and to formulate a taste masked chewable tablet. Kyron T-114 was used as a taste masking agent which was containing cross-linked polyacrylic backbone was used as taste masking agents. The drug resin complex was prepared by complexation of drug with resin using batch method. Maximum drug loading capacity of resins Kyron T-114 was calculated then Drug Resin Complexes were optimized by effect of drug resin ratio, Effect of stirring time. Effect of soaking time, effect of temperature and effect of pH on drug loading. Drug resin complex was evaluated for FTIR studies, drug release at salivary pH 6.8 and dissolution of drug resin

complex at gastric pH. Taste masked chewable tablets of Mebendazole were prepared by direct compression method. Post compression evaluations used such as thickness, diameter, weight variation, hardness, disintegrating test, content uniformity test and *in vitro* dissolution test.

Keywords---mebendazole, kyron T-114, taste masking, ion exchange resin, drug resin complex.

Introduction

The bitter taste of orally delivered drugs frequently leads to patient non-compliance in taking medications, particularly among youngsters and the elderly [1]. Unfortunately, the majority of medications have a bitter flavour that can cause a burning sensation in the throat or mouth. A harsh taste, in particular, can reduce patient compliance, resulting in less effective medication. The use of flavours or sweeteners to create acceptable palatability is limited and may not be effective enough to disguise the taste buds of medications, necessitating the employment of technical procedures. Chewable tablets must be broken and chewed between the teeth before being swallowed. [2]

These chewable tablets are designed to dissolve gently in the mouth at a reasonable rate, either with or without chewing. They have a smooth texture when disintegrated, are pleasant to taste, and leave no bitter or disagreeable aftertaste. In order to make a durable solid dosage form, successful tablet formulation creation necessitates the careful selection of constituents. Choosing the right excipient for a certain function in a tablet formulation, such as disintegration or lubrication, is crucial to achieving good manufacturing results. Sweeteners, both natural and synthetic, are a type of functional excipient that is frequently included in chewable tablet formulations to mask disagreeable tastes and make paediatric dosing easier. They are broken down in the mouth and released their ingredients in the ideal situation when chewed. [3, 4]

Mebendazole is benzimidazole derivative that has been widely used in the treatment of worm infestations in both humans and sintestinal nematode infection. Freely soluble in Formic acid, practically insoluble in water, in dichloromethane, in ethanol (95%) & in ether. Oral bioavailability is 2-10 %. Mebendazole is a benzimidazole derivative with antihelmintic effect. It selectively and irreversibly blocks glucose uptake in the metabolism of nematodes and cestodes. Adult forms in the intestinal lumen, tissue-dwelling larvae, and also helminth eggs of roundworm and whipworm, are affected. The glucose deficiency causes a metabolic disorder that entails the death of the parasite. In humans the drug does not seem to have a clinically relevant influence on the glucose metabolism.[5]

Chemically, KYRON T-114 is Polacrilic acid, and it is made up of cross-linked polymers of Methacrylic Acid and divinyl benzene with H+ functionality, allowing it to be used as a Taste Masking Agent. Basic cationic medicines and associated compounds are carried by the polymer. Good Manufacturing Practices are

followed in the production of the polymer. Kyron T-114 is a hydrogen from cation exchange resin that is insoluble and slightly acidic. Kyron aids in the reduction of medication bitterness. Kyron creates a compound with the active ingredient to create a tasteless medication. As a result, the medication combination is stable at a specific pH. De-complexation occurs in the stomach pH acidic (less than 4 pH) and the drug adsorbs in the blood. As a result, bioavailability is unaffected. The term "taste masking" refers to the perceived diminution of an unpleasant taste. [6]

Materials and Method

Mebendazole was obtained as a gift sample from Syncom Pharmaceutical Industries Ltd., Indore. Resins kyron T-114 was obtained as a gift samples from Corel Pharma Chem., Baroda.

Method

Spectrophotometric Characteristics of mebendazole
Calibration Curve of mebendazole in 0.1 N HCl with 1% SLS

Calibration curve of drug was taken in 0.1N HCL+1% SLS. Absorbance was measured at 234nm using UV visible double beam spectrophotometer. The solutions were prepared in the concentration range between 10 ug/ml to 50mg/ml.

Infrared Spectroscopic Characterization of Drug-Resin Complex

Infrared Spectroscopic Characterization of Drug-Resin Complex was recorded by KBr dispersion technique using FT-IR spectrophotometer. Its gives the confirmation of compatibility of drug and ion exchange resin (Kyron T-114) [7]

Preparation of Drug:Resin Complex

For preliminary study, drug:resin was taken in 1:1 ratio. An accurately weighed quantity of resin was taken in a 100 ml beaker containing 30 ml of deionised water. Resin was allowed to swell for 30 min. Appropriate amount of drug (as per 1:1 ratio) was added into the same beaker and pH of solution was recorded. The beaker was placed on an OSC India magnetic stirrer 900 rpm for 30 min at 30°. After the stirring procedure the solution was filtered using whatman filter paper. The filtrate was analyzed using appropriate dilution for determination of unbound drug at 234 nm using Lab India UV spectrophotometer. The residue on filter paper was dried in a hot air oven at 40°-50°. Percentage of drug bound to resin was calculated from amount of unbound drug. This procedure was performed for all resins separately. [8, 9,10]

Optimization of Drug Resin Complex

The optimization of drug loading capacity of resin was performed by determining the effect of various factors on drug loading. Effect of drug-resin ratio on drug loading was determined. Accurately weighed quantity of Mebendazole was taken and added to the resins (that were selected based on their drug loading capacity)

as per drug-resin ratio of 1:1, 1:1.5, 1:2 and 1:2.5 The resins were previously soaked in 30 ml of deionised water for 30 min. The solutions were stirred using OSC India magnetic stirrer for 900 rpm for 30 min at 30°. The mixtures were filtered and unbound drug in the filtrate was estimated at 234 nm. [11]

Effect of soaking time of resin on drug loading

was determined. Selected resins were soaked in 30 ml of deionised water for 10, 30, 40, 60 and 90 min. Accurately weighed quantity of Mebendazole (as per 1:2.5 ratio) was added to previously soaked resins. The solutions were stirred for 30 min at 40°. The mixtures were filtered and unbound drug in the filtrate was estimated using Lab India UV 3000+ at 234 nm. [12]

Effect of stirring time of resin on drug loading

was determined. Selected resins were soaked in 30 ml of deionised water for 90 min. Accurately weighed quantity of Mebendazole (as per 1:2.5 ratio) was added to previously soaked resins. The solutions were stirred by using magnetic stirrer of OSC India for 5, 10, 30, 60 and 90 min at 40°. The mixtures were filtered and unbound drug in the filtrate was estimated using Lab India UV 3000+ at 234 nm. [12]

Effect of temperature on drug loading

was determined by selected resins were soaked in 30 ml of deionised water for 90 min. Accurately weighed quantity of Mebendazole (as per 1:2.5 ratio) was added to previously soaked resins. The solutions were stirred by using magnetic stirrer of OSC India for 90 min at Room temperature, 30, 40, 50 and 60°. The mixtures were filtered and unbound drug in the filtrate was estimated using Lab India UV 3000+ at 234 nm. [13]

Effect of pH on drug loading

was determined by accurately weighed quantity of Mebendazole (as per 1:2.5 ratio) was added to selected resins that were soaked in 30 ml of solution of pH 2, 3, 4, 4.5, 5, 5.5, 6, 7.5 and 8 (prepared from standard solutions of HCL and NaoH solutions) for 90 min. The solutions were stirred by using magnetic stirrer of OSC India for 90 min at 40°. The mixtures were filtered and unbound drug in the filtrate was estimated using Lab India UV 3000+ at 234 nm. [13]

Characterization and Evaluation of Drug- Resin complex: [14,15,16]

The Drug–Resin Complex was characterized by FT-IR studies using KBr pellet method. The spectra of Drug–Resin Complex was compared with spectra of pure drug (Mebendazole & Kyron T-114)

Dissolution Study of Drug-Resin Complex

An accurately weighted quantity of drug-resin complex equivalent to 100mg of mebendazole was subjected to release study using USP type II dissolution test

apparatus. 10ml Aliquots was withdrawn at time interval of 5,10,15,30 up to 120 minutes and filter the solution by whatman filter paper. The amount of drug was calculated by UV spectrophotmetrically at 234 nm from the calibration curve of mebendazole in 0.1N HCl.

Formulation of Taste Masked Mebendazole Chewable Tablet:[17,18,19]

Drug Resin Complex and all other ingredients were individually passed through a sieve no.72. All the ingredients Starch as binder, sodium starch glycolate as disintegrant, lactose as binder, mannitol as sweetner, sodium saccharin as sweetner, talc as lubricant magnesium stearate as lubricant chocolate flavour as flavour aerosil as thickening agent were mixed thoroughly in a poly bag up to 15 min. The powder mixture was lubricated with magnesium stearate. The tablets were prepared by using direct compression method. Then the blend was compressed using 11 MM flat punch.

Table 1
Formulation of Mebendazole Chewable Tablet

INGREDIENTS In (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
DRC	277	277	277	277	277	277	277	277	277	277
Starch	21	23	25	27	9	12	15	18	21	24
Sodium Starch Glycolate	-	-	-	-	20	19	18	17	16	15
Lactose	80	78	76	74	72	70	68	66	64	62
Mannitol	45	45	45	45	45	45	45	45	45	45
Sodium Saccharide	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Talc	5	5	5	5	5	5	5	5	5	5
Magnesium Stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Chocolate Flavour	3	3	3	3	3	3	3	3	3	3
Aerosil	4	4	4	4	4	4	4	4	4	4
Total	440	440	440	440	440	440	440	440	440	440

Evaluation Mebendazole Chewable Tablets [20,21,22]
General appearance

The general appearance of a tablet its visual identity and overall “elegance” is essential for consumer acceptance. These include tablets size, shape, colour, presence or absence of an odour, taste, surface texture, physical flow and consistency and legibility of any identifying marking. Cross section of press coated tablet was also examined.

Hardness test

Twenty tablets from each batch were individually weighed using electronic digital balance and average weight was calculated. Individual weights of the tablets were compared with the average weight according to the official method in Indian Pharmacopoeia, 2007.

Thickness

The thickness of ten tablets from each batch was determined using vernier calipers as per Indian Pharmacopoeia, 2007

Friability

The friability of the twenty tablets from each batch was determined using Roche friabilator. This device subjects the tablets to the combined effect of abrasions and shock in a plastic chamber revolving at 25 rpm and dropping the tablets at a height of 6 inches in each revolution. A pre-weighed sample (20 tablets) was placed in the friabilator and is subjected to 100 revolutions. Tablets were dedusted and reweighed. The % friability (F) was calculated using following formula:

$$F = (W1-W2 / W1) \times 100$$

Where, W1 is the initial weight of the sample of twenty tablets before the test
W2 is the weight of the tablet after the test

Weight variation test

Twenty tablets from each batch were individually weighed using electronic digital balance and average weight was calculated. Individual weights of the tablets were compared with the average weight according to the official method in Indian Pharmacopoeia, 2007.

Drug Content

20 tablets were accurately weighted and finely powdered. A quantity equivalent to 10mg mebendazole was transferred to a 200ml volumetric flask. 50 ml of methanol was added into it and sonicated and filtered. 20 ml of filtrate diluted to 100ml of methanol and mix. Absorbance of prepared solution was analyzed using LabIndia UV 3000+ spectrophotometer at 234nm

***In-Vitro* Dissolution Test**

In-Vitro dissolution study was carried out (USP Paddle type II) using 900mL, 0.1 N HCL with 1% SLS for 120min. Speed was adjust to 75 RPM and temperature of medium was 37°C. Aliquot (10mL) of the solution was collected from the withdrawn samples were analyze by an UV spectrophotometer at 234nm using HCl buffer pH 1.2 with 1% SLS as a blank.

Accelerated Stability Study

The selected optimized F5 formulation was selected for stability study. The formulation F5 stored at 40°C/75% RH for 3 months and evaluated for their physical appearance, drug content, and dissolution study.

Results and Discussion

Characterization of drug
Calibration Curve of mebendazole in 0.1 N HCl with 1% SLS

Table 2
Absorbance of different concentration of mebendazole at 234nm

Sr.No	Concentration [ug/ml]	Absorbance at 234 nm
1	0	0
2	10	0.210
3	20	0.369
4	30	0.567
5	40	0.801
6	50	0.981

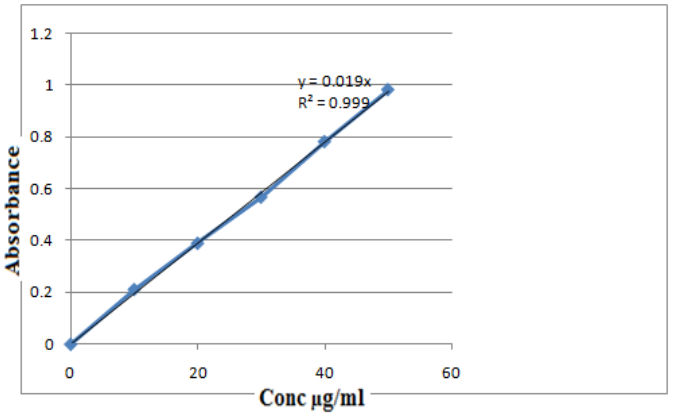

Figure 1. Standard calibration curve of mebendazole in HCl pH 1.2 with 1% SLS

Discussion: It was observed that the graph follow the Beer's- Lambert's law. As the concentration increases the absorbance also increases and the obtained line passed through the zero intercept.

Drug Excipient Compatibility Study

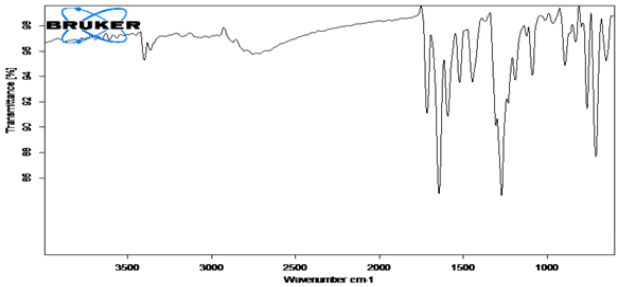

Fig 2. FT-IR Spectrum of Mebendazole

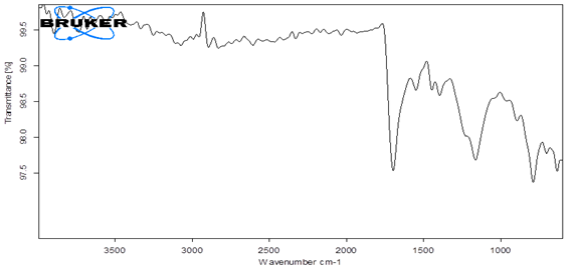

Fig 3. FT- IR Spectrum of KYRON T-114

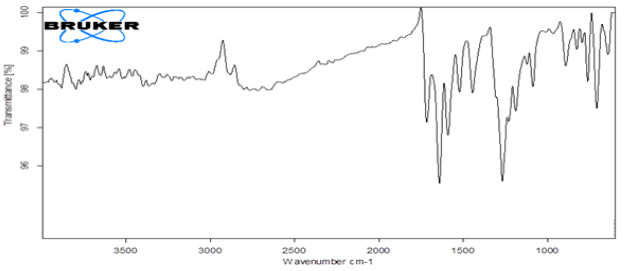

Fig 4. FT- IR Spectrum of Drug Resin Complex (DRC)

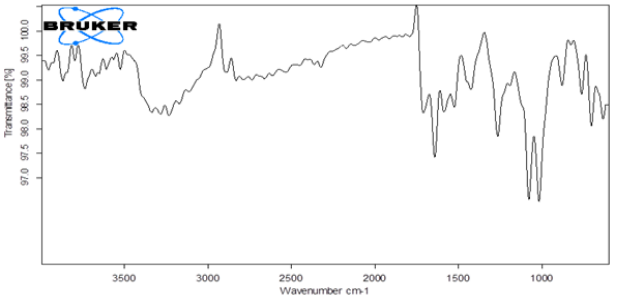

Figure 5. FT-IR Spectrum of Optimised Formulation F5

Discussion: The IR spectrum did not show the presence of any additional peaks for new functional groups and some peaks may be shifted due to presence of moisture indicating no chemical interaction between Mebendazole & excipients used in the formulations. Also the complexation was confirmed by carrying out IR studies which evaluated possible solid-solid interactions between the drug and resin. The IR spectra of complex showed (figure no. 4) that there was no interaction between drug and resin.

Differential Scanning Calorimeter (DSC)

Table 3
Interpretation of DSC of Mebendazole

Sr.No.	Sample	Peak (°C)	Onset (°C)	End set (°C)
1	Mebendazole	254.98	238.30	260.50
2	DRC	236.69	227.13	240.61
3	Optimised Formulation	165.62	163.27	167.77

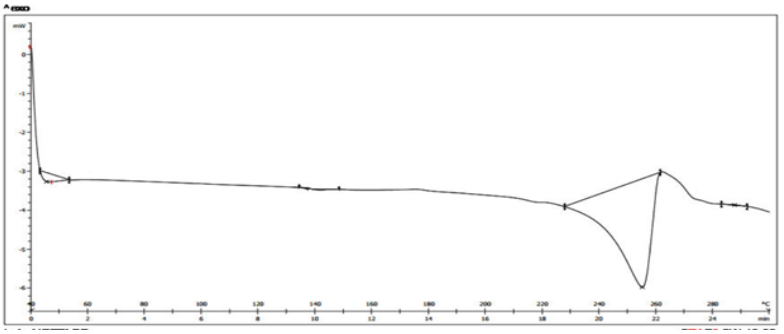

Fig 6. DSC Thermogram of Pure Mebendazole

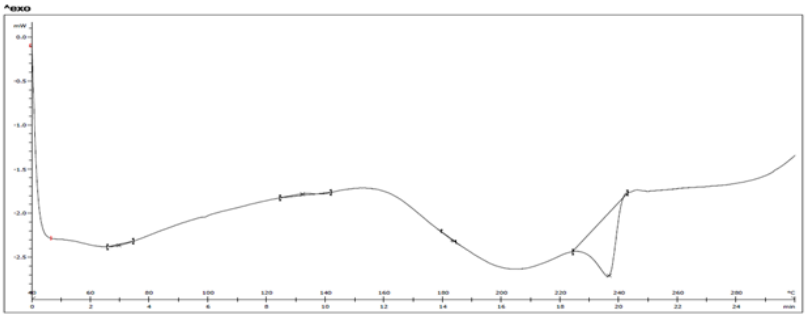

Fig 7. DSC Thermogram of Drug Resin Complex

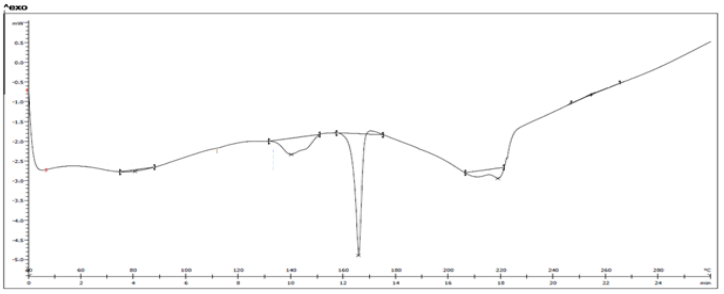

Fig 8. DSC Thermogram of Optimised Formulation(F5)

Discussion: From the above graphs of DSC melting point of Mebendazole, DRC and optimised formulation were determined 254.98 °c., 236.69 °c. and 165.62 °c. Respectively. Thermogram of Mebendazole, excipients and final formulation were recorded as described thermal properties of drug and coated tablet was studied using DSC melting point of drug was observed 254.98°c might changes in crystallinity of drug. Final compatibilities study of Mebendazole with excipients are performed and analyzed. The comparative thermograme of API and final blend results revealed that there was no incompatibilities between them. The clear peak at 254.98°C in the pure API thermogram was not disturbed after final blending was completed.

Optimization of Drug Resin Complex

Table 4
Effect of Drug:Resin Ratio on Drug Loading

Resin	Drug:Resin	Percentage of drug bound to resin (%)
KYRON T-114	1:1	79.4
	1:1.5	83.8
	1:2	87.75
	1:2.5	91.5

Table 5
Effect of Soaking Time on Drug Loading

Drug:Resin	Soaking time (min)	Percentage of drug bound to resin (%)
1:2.5	10	50.67
	30	85.75
	40	87.29
	60	91.52
	90	92.32

Table 6
Effect of Stirring Time on Drug Loading

Drug: Resin	Soaking time (min)	Stirring time (min)	Percentage of drug bound to resin (%)
1.2.5	90	5	36.61
		10	52.49
		30	72.67
		60	88.45
		90	92.5

Table 7
Effect of Temperature on Drug Loading

Drug:Resin	Soaking time(min)	Stirring time (min)	Temperature(°)	Percentage of drug bound to resin (%)
1:2.5	90	90	R.T.	87.54
			30	89.48
			40	91.68
			50	90.37
			60	88.63

Table 8
Effect of pH on Drug Loading

Drug:Resin	Soaking time (min)	Stirring time (min)	Temperature (°)	pH	Percentage of drug bound to resin (%)
1:2.5	90	90	40	2	81.54
				3	83.79
				4	85.44
				4.5	86.29
				5	89.43
				5.5	92.5
				6	88.61
				7.5	87.36
				8	86.54

Discussion: For optimizing drug loading capacity of resin, drug:resin were taken in the ratios of 1:1, 1:1.5, 1:2 and 1:2.5. It was found that, the drug loading efficiency of resin increases as the resin concentration increases, as shown in Table 1.2. Percentage of drug bound to resin was found to be more when drug:resin was taken in the ratio of 1:2.5; since a marginal increase in percentage of drug bound to resin was observed from 1.1.5 to 1.2.5 ratio; the 1:2.5 ratio was selected for further study. Effect of soaking time of resin on drug loading showed that, the percentage of drug bound to resin was found to increase as the soaking time for resin increased. Effect of stirring time on drug loading showed that, the percentage of drug bound to resin was found to increase as the stirring time increased. A marginal increase in percentage of drug bound to resin was observed from 30 to 90 min. Effect of temperature on drug loading was not very significant. Hence, the operational temperature was selected for further study. Effect of pH on drug loading showed that, the percentage of drug bound to resin decreased as the pH decreased. Maximum loading was obtained between pH 4.5–5.5.

Release of drug from Drug Resin Complex
Drug release at salivary pH 6.8

Table 9
Drug release at salivary pH 6.8

Time in Min	% Cumulative drug release
5	0.17%
10	0.18%

Table 10
Dissolution of Drug Resin Complex

Time in Min	% Cumulative drug release
5	19.22 ±0.31
10	25.15 ±0.17
15	29.24 ±0.57
30	37.66 ±0.43
45	46.87 ±0.56
60	57.37 ±0.72
75	69.49 ±0.77
90	76.92 ±0.99
120	85.23 ±0.52

Discussion: The amount of drug released at salivary pH was found to be very less (0.18%). Shown in Table no: 1.7. Thus, the amount of drug released from the DRC at salivary pH indicates its insufficiency in imparting bitter taste in the mouth during administration. Mebendazole release from the DRC was studied in gastric PH of 1.2 ,which showed that the drug release was upto 85.23% within two hours. Thus, the amount of drug released from DRC at gastric pH indicates decomplexation of DRC in presence of gastric fluids and availability of drug for absorption.

Evaluation of Mebendazole Chewable Tablet

Table 11
Physical Evaluation of Mebendazole Chewable Tablet

Formulation	Average Weight (mg) (± SD)*	Thickness (mm) (± SD)*	Hardness (Kg/cm^2) (± SD)*	Friability (%) (± SD)*	Disintegration time (± SD)*	Assay/Drug Content
F1	432±0.21	5.32±0.82	2.5±0.75	1.18±0.21	6±0.25	96.77
F2	431±0.35	5.39±0.35	2.90±22	1.16±0.33	5±0.20	97.54
F3	429±0.32	5.36±0.36	2.8±0.36	1.16±0.65	6±0.35	95.08
F4	434±0.48	5.43±0.39	3.6±0.12	0.9±0.40	5±0.30	95.11
F5	436±0.36	5.36±0.22	3.8±0.30	0.7±.0.66	2±0.34	98.58
F6	433±0.51	5.41±0.96	4.2±0.65	0.6±0.06	2±0.46	97.88
F7	434±0.65	5.34±0.10	3.8±0.05	0.7±0.39	3±0.22	95.45
F8	431±0.38	5.31±0.85	5.2±0.82	0.5±0.85	4±0.55	98.01
F9	434±0.42	5.45±0.88	3.8±0.50	0.6±0.34	4±0.62	96.25
F10	433±0.30	5.38±0.80	5.6±0.37	0.4±0.69	5±0.15	96.07

Discussion: The Compressed tablet was evaluated for values of Average Weight which were found to be in the range of 429 mg ± 0.32–436 mg ±0.36. Thickness for all 10 formulations was found to be in the range of 5.31 mm ± 0.85– 5.45 mm ± 0.88 while Hardness was in the range of 2.5 Kg/cm^2 ±0.75 – 5.6 Kg/cm^2 ± 0.37. The friability of all batches was found to be 0.4% ± 0.69–1.18% ±0.21.

Disintegration time was found to range of 2±0.34 - 6±0.25. The assay of batches from F1-F9 was found in the range of 95.11% to 98.58% complies the pharmacopoeial limits. These above results indicated that the prepared chewable tablets were compiles with reference value. F5 has rapidly disintegrated because it had maximum percentage of disintegrating agent.

Percentage Drug Release of Formulations

Table 12
% Drug Release of Formulation F1 to F10

Time (Min)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
0	0	0	0	0	0	0	0	0	0	0
05	15.20	12.36	9.16	13.65	19.78	20.39	23.42	17.74	11.46	22.47
10	18..36	16.45	13.54	16.17	24.39	23.53	27.1	20.19	19.24	27.46
15	22.64	21.75	17.18	21.69	29.43	28.29	35.16	25.16	26.46	33.20
30	21.69	24.64	21.64	25.49	38.40	38.19	44.13	34.84	34.16	41.06
45	26.89	29.30	23.19	29.17	47.26	44.64	55.12	43.27	45.19	48.50
60	31.65	34.19	28.15	32.48	59.33	57.16	63.82	51.16	52.28	56.09
90	34.12	39.48	30.46	36.14	70.28	64.17	66.42	62.42	61.23	65.27
120	38.49	43.76	34.34	41.36	79.54	73.46	74.10	69.13	68.46	70.84

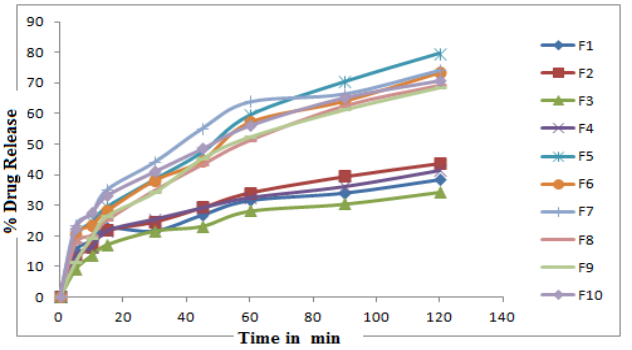

Fig 8. % Drug Release of Formulation F1 to F10

Discussion: In formulations F1- F4 doesn't contains disintegrating agent, but in F5-F10 it contains 4.54%-3.40%. Drug release has found to be 34.34% ± 0.36 – 79.54%±0.84.Formulation F5 has obtained 79.54 % ± 0.84 which maximum drug release

Accelerated Stability Studies

Table 13
Stability Studies for F5 Optimized Batch

Parameters	Initial Data	After 1 month	After 2 month	After 3 month
Appearance	Slightly yellow	No Change	No Change	No Change
Hardness in N	3.8 ± 0.30	3.71±0.10	3.55±0.45	3.51±0.29

Assay (%)	98.42±0.49	98.58±0.72	97.32±0.63	97.20±0.53
% Drug release	79.54±0.84	79.22±0.23	79.09±0.85	79.02±0.62

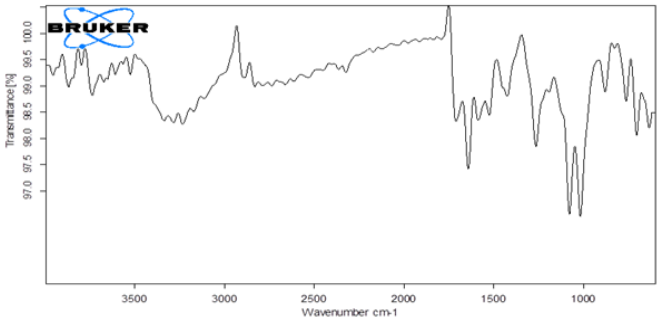

Figure 9. FT-IR Spectrum of Optimised Formulation F5 after 3 months

The stability studies of the chewable tablets (F5) revealed that no significant changes in physical parameters when stored at temperature 45°C and at room temperature. There was also observed that there is no significant reduction in drug content over the period of three month. The IR spectra of complex showed that there was no any interaction between drug and resin hence formulation (F5) was found stable.

Conclusion

The mebendazole having anthlemintic property beneficial to adults and children but in children's the major challenges in chewable tablets are poor patient compliance and bitter taste of formulated product. Prepared formulation mitigate such problem and increase the patient compliance. Prepared formulation also has promising market prospects and satisfied our aim and objective. So we can concluded that Mebendazole can be taste mask by ion exchange resin such as Kyron T-114 with good stability.

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