How to Cite:
Mutha, S., Kshirsagar, C., Shelke, V., & Sawant, S. (2022). Formulation, development and evaluation of chewable tablet of dicyclomine hydrochloride. *International Journal of Health Sciences*, *6*(S7), 1224–1236. https://doi.org/10.53730/ijhs.v6nS7.11430

Formulation, development and evaluation of chewable tablet of dicyclomine hydrochloride

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***Abstract*---**Dicyclomine hydrochloride have major problem to its bitter taste. Due to its bitter taste pediatric and geriatric patients have less acceptability. The objective of present work was preparation and evaluation of chewable tablets of Dicyclomine hydrochloride by using Ion exchange resin for taste masking. Taste masking of Dicyclomine HCl was done by using weak cation exchange resin such as Tulsion 335 and Kyron T 159. When comparing drug loading capacity it noticed that Tulsion 335 showed high drug loading as compared to Kyron T 159 at 1: 5 drug –resin ratio. Maximum drug bounding was observed with 90 min swelling time and 90 min stirring time. Manufacturing of chewable tablet was done by direct compression method. In this formulation various excipients were used such as crospovidone as disintegrant, mannitol as a diluent, Sucralose as sweetener The powder blend and tablet formulation was evaluated for precompression and post compression study respectively. The results have shown maximum drug loading was obtained using Tulsion 335 as ion exchange resin in the ratio of 1:5 (drug: resign). Taste masking was evaluated with invitro threshold value. Powder blend passes all precompression parameters The tablet prepared with powder blend formulation found to be smooth rounded shape without imperfections. These tablets were evaluated for post-compression parameter. The tablet pass the weight variation test as standard deviation observed

was ±7.06 % which was within the 10 % limit The wetting time was found to be 41±1.5 seconds. The water absorption ratio was found to be 81±1.5 % was excellent Uniform drug content observed for these chewable tablet 99.53±1.09 percent. The % release was found to be 97.40 % in 8 min. The release data indicated zero order release pattern. The release rate and the pattern indicated the suitability of the dosage form. Thus all the post-compression parameter studied were in the acceptable limits The outcome of work recognized a unique, simple, and stable product having improved taste masking and patient friendly, quick release dosage form for Dicyclomine hydrochloride.

***Keywords*---**Chewable tablet, Tulsion 335, Kyron T 159, ion exchange resin, taste masking

Introduction

Dicyclomine hydrochloride is an antispasmodic drug which is widely used in treatment of smooth muscle spasm of the gastrointestinal tract[1]. Dicyclomine hydrochloride have major problem to its bitter taste. Due to its bitter taste pediatric and geriatric patients are not acceptable. So there is need to be formulated into the fast release dosage form[2]. In conventional tablet onset of action is slow. Thus due to all above mention properties, dicyclomine hydrochloride was selected as the candidate for chewable tablet. The chewable tablet is a solid dosage form that disintegrates smoothly in the mouth without the need of water. Pre gastric absorption through mouth, pharynx, esophagus could enhance the bioavailability of drug as drug get dissolve in saliva and passes down to the stomach[3]. Chewable tablets are usually formulated for patients who have complicity or problem in swallowing tablets. These categories of patients may be adults with throat infection or infants and children who have not learned how to properly swallow tablets with liquid.[4,5]

Dicyclomine hydrochloride is available as a tablet and suspension formulations in the market Chewable tablet of dicyclomine hydrochloride is designed in order to improve its bitter taste, fast onset of action, improves bioavailability, improves patient compliance. Chewable tablet form of dicyclomine hydrochloride is not available in market till date, here attempts are made to develop and evaluate it.

Materials and Methods

Materials

Dicyclomine hydrochloride was received as a gift sample from Wockhardt Research Centre, Aurangabad. Tulsion 335 and Kyron T 159 were procured from FMC Biopolymer, Mumbai. Crosspovidone , Mannitol, Vanillin, Sucralose, Magnesium stearate, Aerosil were purchased from Research-Lab Fine Chem Industries, Mumbai

Methods of preparation of resinate:

Resins were purified using the method reported by Irwin et al. The resins were washed successively with distilled water, 0.1 N HCL and 0.1 N NaOH in separate processes for activation. The resin was repeatedly washed with 50ml water until neutral pH was reached. All resins were dried at room temperature and kept in an amber glass vial[6].

Preparation of Drug-resin complexes (DRC):

DRC were prepared by adding 100 mg of activated resin that was swollen for 60 min in a beaker containing 50 ml distilled water, 100 mg of drug was added separately into each of the beaker containing the activated resin, to prepare slurry with the aid of magnetic stirrer for 90 min at 60°C. Filter the reaction mixture by Whatmann filter paper. Collect the residue & wash with 100ml distilled water. Allow the washed complex for drying on room temperature for 2-3 hrs. From the filtrate 1ml was taken and diluted to 10 ml with distilled water[7]. The unbound drug in the filtrate was estimated spectrophotometrically at 213 nm. The rate of addition of drug to resin slurry had profound effect on the taste masking and free drug concentration of drug-resin complex. Slow addition of drug showed low % of free drug in the mixture and better taste masking while fast addition showed high % of free drug in the mixture and poor taste masking of drug-resin complex. Optimum taste masking was found when rate of addition was slow. Drug was added with constant time interval of 4-5 minute

Optimization of resin concentration for maximum drug loading:

Different quantities of activated resins to obtain resin: drug ratios of 1:1, 1:2, 1:3, 1:4 and 1:5 were placed in different beakers containing adequate quantities of distilled water and allowed to swell for 60 min. Hundred mg of drug was added and stirred using a magnetic stirrer for 90 min at 60°C. The mixtures were filtered and residues were washed with adequate quantities of distilled water. The drug-loading efficiency of the resin was estimated . The ratio of resin: drug revealing maximum loading of drug was the optimized ratio.

Optimization of swelling time of resin for maximum drug loading:

Separate batches of activated resins were soaked in adequate quantity of distilled water for 60, 90 and 120 min at 60°C. The swelling time required for maximum drug loading was optimized.

Optimization of stirring time for maximum drug loading:

Separate batches of acid-activated resins were soaked in adequate quantity of distilled water and drug was added and stirred for 60, 90 and 120 min with the aid of a magnetic bead at 60°C. Resin drug loading efficiency was estimated. The time required for maximum drug loading was thus optimized[3]. Depending on the results of resin optimization study; batches of drug-resin mixtures at ratios 1:1, 1:2, 1:3, 1:4 and 1:5 were prepared as previously discussed at optimized conditions for % drug loading capacity

Preparation of tablet:

The formulation of chewable tablet of dicyclomine hydrochloride done by using selected DRC mixture. Tablets were prepared by direct compression method using crospovidone as disintegrant, mannitol as a diluent, Sucralose as sweetener[8]. Attempts were done to reduce the bitter taste of the tablet more comfortable and acceptable administration. All the materials were precisely weighed, transferred to mortar, mixed and passed through a sieve no 60. Then the blend of powder was compressed into the tablet by a rotary mini-press tablet punching machine. The weight of tablet is 250 mg. The formulated tablets were evaluated for taste masking potency. Only optimized batch was taken for compression.

Table1
The compositions of chewable tablets of dicyclomine hydrochloride

Ingredients	**Weight (mg)**
DRC equivalent to20 mg	120
Crospovidone	25
Mannitol	80
Aerosil	5
Sucralose	8
Vanillin	2
Magnesium stearate	10
Total weight	**250**

Evaluation Parameters:

Evaluation of Taste masked resinate

Taste masked resinate evaluated for taste masking potency. DRC equivalent to 20 mg of dicyclomine hydrochloride were placed in a 25ml volumetric flask. To this, 20 ml of simulated salivary fluid (SSF) was added and shaken for 60 sec. and then filter the solution. The appropriate concentration was made by dilutions. The amount of dicyclomine hydrochloride released was analyzed by UV visible spectrophotometer and analyzed at 213nm by UV-Visible spectrophotometer and that was compared with the threshold value[9,10]

Precompression parameters evaluation [11,12]

Bulk density

It was determined by pouring pre sieved drug excipient blend into a 100 ml graduated cylinder. The sample occupied volume and its weight has been recorded It is expressed in g/mL and calculated by using following formula:

$$\rho b = M / Vp \quad \ldots\ldots (1)$$

Where, ρb = Bulk density

M = Weight of sample in grams

Vp = Final volumes of Powder in cm3

Tapped Density

It was carried out by pouring powder blend in 100ml graduated cylinder. The cylinder was tapped mechanically by Tap density apparatus until a constant volume was obtained. Volume occupied by the sample after tapping were recorded and tapped density was calculated by using following formula:

$$\rho t = M / VT \quad \ldots\ldots (2)$$

Where, ρt = Tap density
M = Weight of sample in grams
VT = final tap volume of powder in cm3

Car's Index (Compressibility Index)

It is also one of the simple methods to evaluate flow property of a powder by comparing the bulk density and tapped density. The percentage compressibility of a powder is a direct measure of the potential powder arch or bridge strength and stability. It can be calculated by following formula:

$$\text{Carr's Index} = (\text{Tapped density} - \text{Bulk density})/(\text{Tapped density}) \times 100 \quad \ldots\ldots (3)$$

Hausner's ratio

It is the ratio of tapped density to bulk density. It was calculated by the following formula:

$$\text{Hausner's ratio} = \text{Tapped density} / \text{bulk density} \quad \ldots\ldots (4)$$

Angle of repose

Flowability of blend was determined by calculating angle of repose by fixed height method. funnel with 10 mm inner diameter of stem was fixed at a height of 2 cm over the platform. The sample was slowly passed along the wall of the funnel till the tip of the pile formed and touches the stem of the funnel. A rough circle was drawn around the pile base and the radius of the powder cone was measured. Angle of repose was calculated from the average radius using the following formula:

$$\theta = \tan^{-1}(h/r) \quad \ldots. (5)$$

Where, θ = angle of repose,
h = height of pile,
r = average radius of the powder cone.

Post compression parameters[13]

Hardness

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Digital hardness tester. It is expressed in Kg/cm2. Digital hardness tester was used to measure

hardness of the tablet. In which the tablet was placed in the tester and pressure needed to break the tablet was measured.

Thickness

Ten tablets from formulation batch were used and average values were calculated. Thickness was measured by using Vernier calipers and expressed in mm.

Friability

Friability is the measurement of tablet strength. Roche friabilator (FT1020, Lab India) was used for testing the friability using the following procedure. 10 tablets were weighed accurately and placed in the tumbling apparatus that revolves at 25 rpm for 4 min, dropping the tablets through a distance of six inches with each revolution. After 100 revolutions, the tablets were weighed and the % friability was calculated measured using the formula:

% Friability=(Initial weight of tablet-Final weight of tablet)/(Initial weight of tablet)×100…. (2.5)

Wetting time

In that the tissue paper has been folded twice and placed in petri dish above that tablet is placed. A small quantity of amaranth red color was put on the upper surface of the tablet and 10 ml distilled water was added. The time required to get the tablet completely wet and indicate red color was measured.

Water absorption ratio

In that the tissue paper has been folded twice and placed in petri dish above that tablet is placed. A small quantity of amaranth red color was put on the upper surface of the tablet and 10 ml distilled water was added and allowed to tablet complete wet. The wetted tablet is then weighed and absorption ratio calculated by following formula:

$$\text{Water absorption ratio} = \frac{wa - wb}{wa} \times 100$$

…. (6)

Where, Wa – weight of tablet after absorption
Wb – weight of tablet before absorption

Weight Variation

Weight variation was calculated as per method described in Indian pharmacopeia (I.P.2007). 20 tablets were weighted individually by using Electronic balance (Shimatzu) and the average weight is calculated. The tablets meet the test if no more than 2 tablets are outside the percentage limit and no tablet differs by more than 2 times the percentage limit..

Drug Content

This method is performed as per Indian Pharmacopoeia. Two tablets were crushed and added to 30 ml of 0.1M NaOH in 100 ml volumetric flask sonicated to

disintegrate, then diluted by acetonitrile, then these solution was filtered and diluted the filtrate with a mixture of seven volumes acetonitrile and three volumes of 0.1M NaOH. Absorbance was measured by UV spectroscopy at 213nm and drug content was calculated.

***In vitro* drug release study**

In vitro drug release of tablet was carried out using USP dissolution testing apparatus II(Paddle). The dissolution testing was carried out using 900ml 0.1 N HCL at 37^0C and 50 rpm. A sample 5 ml was withdrawing at 2,4,6,8,10 min. The sample was replacing with fresh dissolution medium of same quantity. Sample was analyzed at 213 nm by using UV-spectrophotometer[14].

Taste Evaluation

Some quantity of the taste masked formulation is mixed with 10 ml of distilled water in 10 ml syringe by rotating the syringe, 5 times in 30 seconds. The test medium is then filtered with the help of a membrane filter, the and determine the concentration of the drug in the filtrate spectrophotometrically. If this concentration is under the threshold concentration, it may be assumed that the bitter taste would be masked in vitro[15].

Comparison of In-vitro dissolution study of dicyclomine hydrochloride chewable tablet with marketed tablet

Marketed formulation of dicyclomine hydrochloride (Declor 20mg) manufactured by Health Guard Pvt Ltd was taken for in-vitro comparison with dicyclomine hydrochloride chewable tablet

Results

Preparation of Drug-resin complexes (DRC):

Taste masking done by using ion exchange resin with batch method. IER are solid and suitably insoluble high molecular weight polyelectrolytes that can exchange their mobile ions of equal charge with the surrounding medium. Being high molecular weight water insoluble polymers, the resins are not absorbed by the body and are therefore inert[5]. Weak cationic exchange resins of Tulsion 335 and Kyron T 159 were tried in different ratios drug and resins respectively[16]. After complexing it was evaluated for % drug loading capacity. Then this DRC transferred into compression blend[17].

Optimisation of resin concentration for maximum drug loading

From the different DRC, the one was selected on the basis of % drug loading capacity. The Drug resin complexes were prepared by batch method which characterized maximum drug loading. The amount of drug loaded onto the resin was higher with increasing resin concentration; the maximum amount of drug loaded was found to be 93.12±0.07 in the ratio 1:5 for Tulsion 335 resin and for Kyron T159 shows 74.15±0.11. When comparing both drug loading capacity it

noticed that Tulsion 335 show high drug loading as compared to Kyron T 159 as shown below table. This can be explained by the stoichiometric nature of the exchange reaction between drug and resin in solution[9,18].

Table 2
The drug loading based on drug: resin ratio

Drug :resin ratio	% of drug bound to resin (Tulsion 335)	% of drug bound to resin (Kyron T 159)
01:01	81.06±0.58	64.14±0.1
01:02	85.89±0.38	66.10±0.38
01:03	87.11±0.55	68.15±0.05
01:04	92.08±0.34	70.06±0.08
01:05	93.12±0.07	74.15±0.11
01:06	93.03±0.07	74.06±0.13

Optimization of swelling time & stirring time of resin for maximum drug loading:

The swelling and hydration properties of resin is significantly affects the rate of the exchange reaction. These type of reaction is greatly affected by stirring time where the percentage of loaded drug was increased by increasing stirring time and rate of addition of drug is slow (4-5min). The optimized percentage drug loading (w/w) was found to be 93.60±0.07and 74.0±0.15 at swelling time of 90 min and stirring time also 90 min for Tulsion 335 and Kyron T 159 respectively in the ratio of 1:5. When comparisons were made between this two resins then obtained results shows that Tulsion 335 is good candidate than Kyron T 159 for taste masking of Dicyclomine hydrochloride. Therefore, for further study DRC of Tulsion 335 was used[19].

Table 3
The drug loading based on swelling time and stirring time

Batches	Swelling time (min)	Stirring time (min)	% of drug bound to resin (Kyron T 159)	% of drug bound to resin (Tulsion335)
F1	60	60	64.11±01	87.5±0.07
F2	60	90	65.12±0.15	88.2±0.38
F3	60	120	68.14±0.21	87.9±0.61
F4	90	60	71.01±0.09	88.1±0.81
F5	90	90	74.10±0.08	93.60±.0.07
F6	90	120	73.0±0.15	90.4±0.49

F7	120	60	70.09±0.05	89.5±0.65
F8	120	90	71.05±0.12	89.7±1.16
F9	120	120	72.11±0.09	90.3±0.47

Evaluation of pre-compression and post-compression parameter of chewable tablet

The pre-compression parameter plays an important role in tablet. The DRC transferred into compression blend. In compression blend, mannitol used as bulking agent, Crosspovidone as disintegrant, magnesium stearate as lubricant.The angle of repose of powder blend was found to be 27.81^0±0.56 which is in the range of 25 – 30^0 which indicated excellent flow property. Bulk density was found to be 0.37±0.005 gm/ml and Tapped density was found to be 0.41±0.044 gm/ml. The flow property was confirmed with a carr's index observed 8.5±0.047 % (range is 5 – 10 %) indicated excellent flow property. Hausner's ratio of 1.09±0.01 also showed excellent flow property within the acceptable limits[17,20]. All the pre-compression parameters of powder blend of selected chewable tablet are shown in below table

Table 4
Precompression parameters of drug resin powder blend

Sr. no.	Precompression Parameters	Observations
1	Angle of repose	27.81^0±0.56
2	Bulk density	0.37±0.005 gm/ml
3	Tapped density	0.41±0.044 gm/ml
4	Car's Index	8.5±0.047 %
5	Hausner's ratio	1.09±0.01

Evaluation of post-compression parameter of chewable tablet

The tablet prepared with powder blend formulation found to be smooth rounded shape without imperfections. These tablets were evaluated for post-compression parameter. The tablet pass the weight variation test as standard deviation observed was ±7.06 % which was within the 10 % limit. Thickness was found to be 3.1±0.2 and hardness was 2.6±0.06. Friability was also found to be 0.5±1.2 which was less than 1 % indicated suitability of the tablet for the transportation. The wetting time showed that prepared chewable tablet completely wetted in minimum time. Less wetting time gives faster disintegration. The wetting time was found to be 41±1.5 seconds. The water absorption ratio showed that quantity of water absorbed by the chewable tablet. If the water absorption is high, then tablet will disintegrate fast and easily. The water absorption ratio was found to be 81±1.5 % was excellent. A fundamental quality attribute for all pharmaceutical preparations is the requirement for a constant dose of drug between individual tablets. Uniform drug content observed for this chewable tablet 99.53±1.09 %

which was as per IP 2010 (Specification 98 – 102 %). All the post-compression parameter studied were in the acceptable limits[11,21]

Table 5
Post-compression parameters of chewable tablet formulation

Sr. no.	Post compression parameter	Observations
1	Weight variation	99.25±7.06
2	Thickness (mm)	2.6±0.06
3	Hardness (kg/cm2)	3.1±0.2
4	Friability (%)	0.5±1.2
5	Wetting time (Sec)	41±1.5
6	Water absorption ratio (%)	81±1.5
7	Uniformity of drug content (%)	99.53±1.09

In-vitro Dissolution study

The % release was found to be 97.40 % in 8 min as shown in Figure1. The release data was fitted in the different kinetic release model which indicated zero order release pattern with R2 value 0.0998 and K as 1.875. The release rate and the pattern indicated the suitability of the dosage form[22]

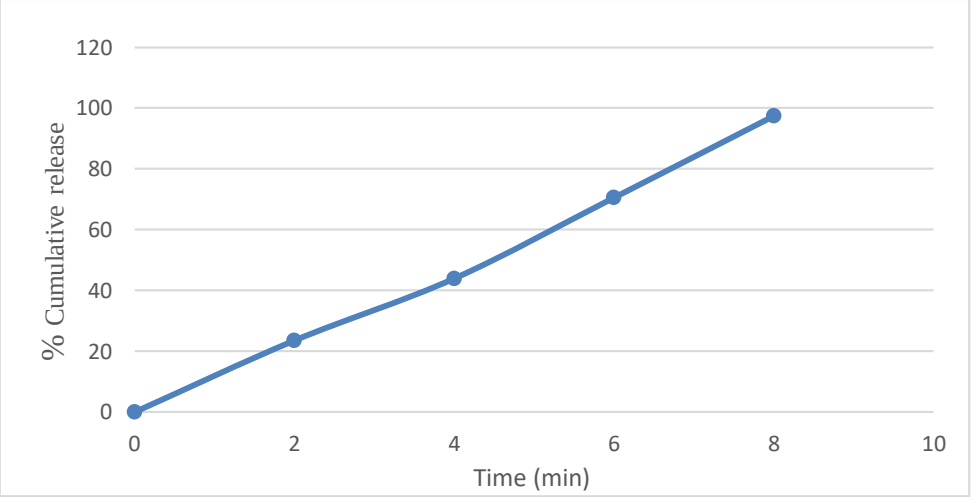

Figure 1. In vitro dissolution data

Taste evaluation

Taste masking potency is a major consideration for chewable tablet. To reduce bitter taste is an added advantage of formulation for maximum absorption and compliance by the patient. It was found that bitterness of tablet is reduced

corresponding bitterness threshold of Dicyclomine hydrochloride. Taste evaluation done by UV-Visible spectrophotometer which was compared with the threshold value and found to be below threshold value[21,23,24].

Comparison of In-vitro dissolution study of dicyclomine hydrochloride chewable tablet with marketed tablet

The dissolution data revealed that formulated chewable tablet showed the rapid drug release about 70.54 % in 6 min and 97.40 % in 8 min while the marketed tablet of dicyclomine hydrochloride (Declor 20 mg) showed 9.36 % drug release in 6 min and 98.71% in 18 min. Fast release was observed with formulated tablet.

Conclusion

Ion exchange resin Tulsion335 was observed to impart good taste masking as compare to Kyron T 159. Additionally, it can be concluded that the swelling time and stirring time factors are important along with drug: resin ratio to have maximum taste masking. The formulation of dicyclomine Hydrochloride chewable tablet is found to give good taste masked formulation along with fast release of medicament as compare to marketed formulation.

Conflict of interest:

The authors have no conflicts of interest regarding this investigation**.**

Acknowledgments

The authors would like to thank Wockhardt Research Centre, Aurangabad for their kind support.

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