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RESEARCH ARTICLE

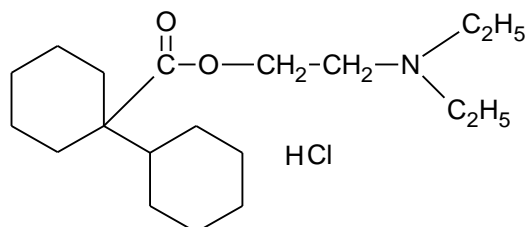
TASTE MASKING EVALUATION AND FORMULATION OF DICYCLOMINE HYDROCHLORIDE SUSPENSION USING ION EXCHANGE RESINS¹Abdul Mannan Khan & ²Farhan Jalees Ahmed¹Institute of Pharmacy, Shri JTT University, Jhunjhunu Rajasthan, India-333001²Department of Pharmaceutics, Jamia Hamdard College of Pharmacy, Jamia Hamdard University, New Delhi, India**ABSTRACT**

There are number of drugs that are bitter and unpleasant in taste and taking orally very difficult for children and some adults. Non-compliance can lead to many problems in diseased condition. There are lots of taste masking technologies have been used to address the problem of patient compliance. The purpose of this research was to mask the intensely bitter taste of Dicyclomine HCl and to formulate a palatable liquid formulation of the taste-masked drug, by novel Ion Exchange Resin (IER) method to overcome taste problem with traditional system. Taste masking was done by complexing Dicyclomine HCl with Tulsion 335, Indion 254 and Indion 414 in different ratios. Formulation containing resinsates were tested for drug content, in vitro drug release, taste masking, stability study, and molecular property. The resinsates prepared with drug- Indion 254 ratio (1:2) at pH 8, gave maximum drug loading. Suspension containing above resinsates showed more than 80% In vitro drug release within 30 min. Prepared formulation also showed good stability and can retain its palatable taste. Thus, the "patient-friendly dosage form" of bitter drugs, especially for pediatric, geriatric, bedridden, and noncooperative patients, can be successfully formulated using this technology.

Keyword: Taste Masked Suspension, Dicyclomine HCl Taste masking, resinate

1. INTRODUCTION

Dicyclomine HCl is mainly used as antispasmodic and antiulcer drug. This is mainly anticholinergic. The drug is used in sever spasm of stomach in stomach pain. Dicyclomine HCl is bitter in taste so the drug is prepared with the use of ion exchange resin to mask the taste of active drug. The drug is given as an oral tablet is rapidly and well absorbed from the gastrointestinal tract after oral administration. The absolute bioavailability is approximately 70% with no substantial loss by first pass metabolism A 500 mg oral dose given every 12 hrs has been shown to produce an area under the serum concentration time curve(AUC) equivalent to that produced by an intravenous infusion of 400mg is given over 60min every 12hrs.

**Dicyclomine HCl****Figure 1:** Structural formula of Dicyclomine HCl

Novel drug delivery technologies are revolutionizing drug discovery and development. The challenge in the area of drug delivery is to deliver both existing and

emerging drug technologies in a manner that benefits patients.

Good mouth feel of formulation helps to change the basic view of medication from "bitter pill" to "better pill". Taste is one of the most important parameters governing patient compliance. Undesirable taste is one of several important formulation problems that is encountered with certain drugs. Oral administration of bitter drugs with an acceptable degree of palatability is a key issue for health care providers, especially for pediatric patients. Also, such pharmaceutical preparations used for elderly patients have been investigated to improve the treatment compliance and quality of life of such patients. Thus, the problem of bitter and obnoxious taste of drug in pediatric and geriatric formulations is a challenge to the pharmacist in the present scenario.

Patient expects the oral dosage form to be pleasantly flavored and palatable. This change in patient attitude is due to the advances made by flavoring and pharmaceutical industries. Several oral pharmaceuticals and bulking agents have unpleasant, bitter-tasting components. Thus, any pharmaceutical formulation with a pleasant taste would definitely be preferred over another product and would translate into better patient compliance and therapeutic value. The desire of improved palatability in these products has prompted the development of numerous formulations with improved aesthetic appearance and performance.

The application of drug delivery technology to any molecule is based on market needs, product differentiation, and patient compliance. The time to get the new chemical entity to the market eats up a majority of the patent life cycle of the drug. Taste masking technologies are very helpful in adding value/timeline to the patent.¹⁻¹⁰

2. MATERIALS AND METHODS

2.1 Materials:

Dicyclomine HCl was gift sample from Sun Pharma Ltd., (Jammu, India). Tulsion 335 and Indion 254 was obtained as gift sample from Corel Pharma Chem, (Ahmedabad, India). Indion 414 purchased from Ion exchange India limited (Mumbai, India). Sucrose, sorbitol, glycerine, xanthane gum, aspartame, methyl paraben and mango candy flavour were purchased from S. D. Fine chemicals (Mumbai, India). All other chemicals/solvents were of analytical grade.

2.2 Methodology:

2.2.1 Purification of ion exchange resin

Resins were purified using the method reported by Irwin et al.¹². The resins (5 g) were washed successively with distilled water, methanol (50 ml), benzene (50 ml),

methanol (50 ml) and several times with distilled water to eliminate organic and color impurities. Then, the wet resins were activated by 0.1 M HCl 50 ml and washed several times with distilled water. All resins were dried overnight in hot air oven at 50°C and kept in an amber glass vial.

2.2.2 Preparation of drug – resin complex

Drug-resin complex were prepared by batch process. Step 1: Weigh all the ingredient accurately. Now add weighted quantity of resin in specific quantity of water and stir it for 15 min. under mechanical stirrer. Step 2: Now add weighted quantity of Dicyclomine HCl into step 1 & stir it for 4 to 5 hr. continuously under stirrer. Step 3: Take specific quantity of water boil it dissolve sugar & filter it. Now cool the syrup at room temperature and add sorbitol and glycerin in it & add into step 2 under continuous stirring^{13, 14, 15}. Step 4: Take water & add xanthane gum and stir it to form a paste. Add this paste in step 3 slowly under stirring. Step 5: Take warm water dissolve methylparaben, propylparaben & aspartame in to it & add in to above solution under stirring. Step 6: Now add coloring, flavoring agent in step 5 & make volume of suspension up to required quantity by using purified water, pH of resin solution was adjusted to 8 by using 1 M KOH¹⁶.

Table 1: Formulation of Dicyclomine HCl suspension with different resins

Ingredients	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10
Complex formation										
Dicyclomine HCl [mg]	500	500	500	500	500	500	500	500	500	500
Tulsion 335	300	600	900	-	-	-	-	-	-	-
Indion 254	-	-	300			300	600	-	-	
Indion 414	-	-	-	-	-	-	-	300	600	900
Purified water	25	25	25	25	25	25	25	25	25	25
Surup preparation										
Sucrose [gm]	2.25	2.25	2.25	2.25	2.25	2.25	2.25	2.25	2.25	2.25
Glycerin [ml]	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Xanthan gum [mg]	20	20	20	20	20	20	20	20	20	20
Methyl paraben [mg]	10	10	10	10	10	10	10	10	10	10
Propyl paraben [mg]	4	4	4	4	4	4	4	4	4	4
Aspartame [mg]	15	15	15	15	15	15	15	15	15	15
Mango candy flavor	0.13	0.13	0.13	0.13	0.13	0.13	0.13	0.13	0.13	0.13
Quinoline yellow color	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Purified water [ml]	5	5	5	5	5	5	5	5	5	5

2.2.3. Evaluation of taste masked suspension

(a) Determination of drug content in resonates:

Dicyclomine HCl resinate (50 mg) was placed in a beaker to which 0.1N HCl (50 ml) was added for eluting Dicyclomine HCl from the resinate¹⁷. The volume of

eluate was measured and assayed for the content of Dicyclomine HCl by spectrophotometry at wavelength of 272 nm.

(b) In-vitro release of suspension:

Dissolution studies of above samples were performed

using USP XXIII apparatus type 2. Suspension equivalent to 400 mg of the drug were added to the dissolution medium (500 ml 0.1N HCl at a temperature of $37 \pm 0.5^\circ\text{C}$), which was stirred with a rotating paddle at 50 rpm¹⁸. At suitable time intervals, 10 ml samples were withdrawn, filtered (0.22 μm), diluted and analyzed at 272 nm using UV spectrophotometer

(c) Determination of Viscosity:

The viscosity of gel was determined at ambient condition (DV III+, Brookfield Programmable Rheometer) using adequate amount of the sample¹⁹.

(d) Taste Evaluation:

The taste of suspension was checked by panel method. The study protocol was explained and written consent was obtained from volunteers. For this purpose, 10 human volunteers were selected¹⁷. About 5 ml suspension containing 500 mg of drug was placed on tongue and taste evaluated after 15 s. Take 10 ml of suspension in 100 ml volumetric flask & make up the volume up to 100 ml with 0.1N HCl. Now take 2 ml solution from flask & add in to 200 ml volumetric flask. Make up the volume up to 200 ml with 0.1 N HCL filter it & measure the absorbance at wavelength 277 nm in U.V. Spectrophotometer & compare it with standard. Calculate % drug content by using following formula.

(f) Sedimentation volume:

Sedimentation volume (F) is a ratio of the final or ultimate volume of sediment (H_u) to the original volume of sediment (H_o) before settling. It can be calculated by following equation.

$$F = \frac{H_u}{H_o} \text{----- (1)}$$

Where, H_u = final or ultimate volume of sediment

H_o = original volume of suspension before settling.

(g) Accelerated Stability Study:

Suspensions were packed in 60 ml glass bottle. The packed bottles were placed in stability chamber maintained at $40 \pm 2^\circ\text{C}$ and $75 \pm 5\%$ RH for 3 month. Samples were collected at days 0, 5, 15, 30, 60 and 90. The analyses comprised chemical testing of quantifiable parameters, which could possibly change during storage, such as viscosity, pH, drug contents, sedimentation volume, redispersibility, taste and any kind of microbial or fungal growth^{14,20}.

3. RESULT AND DISCUSSION

For preparation of resins, batch method was preferred because of its convenience. Equilibrium was reached within 6 h. The high affinity of resins to hydrogen ions can yield fast desorption of bound ions when they are exposed to an acidic environment such as the stomach. When the pH is lower than 4, the resin exists in the Free State. Therefore, drug/resin complex formation needs to be carried out at pH 6 or higher. Higher concentration of competing ions at

lower pH may inhibit the interaction of resins²¹. At pH 8 maximum loading of Dicyclomine HCl was seen onto Tulsion 335, Indion 254 and Indion 414 (data not shown). Effect of drug: resin ratio on % drug content per gram of resinate are shown in [Table 2]. It shows that for Tulsion 335 and Indion 254 maximum drug loading were observed at 1:2 drug resin ratio while 1:1 was observed for indion 414. As the cross linking ratio and particle size increased, the drug loading and release rate decreased due to the reduced effective diffusion coefficient and surface area. When the resin is highly cross linked, fewer functional groups are available inside the particle, resulting in low ion-exchange capacity^{22,23}.

Table 2: Evaluation parameter of Dicyclomine HCl suspension with different resins

Parameters	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10
Drug loading of dry resinate	-	32.15	41.46	42.28	39.42	43.95	46.42	39.58	38.45	43.25
Color	Pale	Pale	Pale	Pale	Pale	Pale	Pale	Pale	Pale	Pale
Viscosity	298.2	296.58	302.45	304.23	296.25	304.58	300.52	297.42	304.2	306.
pH	7.8	8	7.6	8	7.9	7.5	8.1	7.8	7.8	8
Sedimentation volume	0.98	0.97	0.95	0.97	0.98	0.96	0.92	0.95	0.93	0.96
Redispersibility	++	++	+++	++	++	+++	+++	++	++	++
Assay	99.47	100.02	99.75	99.88	100.65	99.58	99.98	98.96	100.1	99.87

Results of taste evaluation by panel method [Table 3] revealed that Tulsion 335, Indion 254 and Indion 414 mask the bitter taste of drug completely at 1:2 and 1:2.5 ratios.

Table 3: Evaluation of taste of suspension

Code	Volunteers									
	1	2.	3.	4.	5.	6.	7.	8.	9.	10.
	3	2	3	3	2	3	3	2	3	3
C2	2	2	3	1	0	2	1	0	3	1
C3	1	2	0	1	0	3	2	1	2	0
C4	0	1	0	2	3	1	2	1	3	0
C5	20	1	3	2	1	0	1	3	2	2
C6	1	2	0	1	2	1	3	2	0	1
C7	0	3	1	2	3	0	2	1	2	3
C8	2	0	2	1	2	1	2	3	1	0
C9	1	2	1	3	1	2	1	0	2	1
C10	2	1	2	0	3	2	1	0	3	2

0 = normal, 1 = slightly bitter, 2 = bitter, 3 = very bitter

In vitro release profile of resins prepared using different resins is shown in [Figure 2]. Study was carried out in 0.1 N HCL using USP paddle apparatus at 50 rpm. More than 80% of drug was released within 30 min from C7 formulation. In general, strong acid type resins showed greater sustained release than weak acid type resins in in vitro dissolution tests^{17,24}. In general, drug is released from the resin by exchanging with ions in a surrounding release medium, followed by drug diffusion

through the polymer matrix of the resins. Some drug molecules released accumulated around the surface of the resins to form an aqueous boundary layer. Stirring can be introduced to the diminish this layer. However, higher cross linked resins display a more sustained release effect than lower cross linked resins. Slight distinction between release profile of formulations may be due to various cross linking ratio of resins.

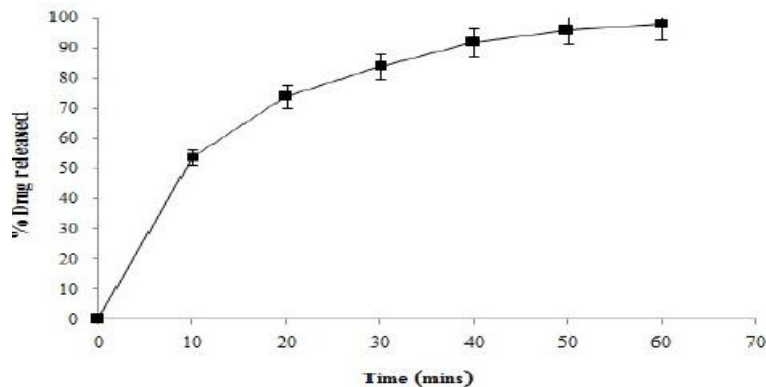


Figure 2: In vitro dissolution profile of D7 (Dicyclomine HCl-Indion 254, 46.3% drug loading)

Accelerated stability study of C7 is shown in [Table 4]. Study revealed that prepared formulation (C7) can be remaining intact for a long period of time without major changes in assay, viscosity and sedimentation volume. It was found that formulation was remained palatable without any appearance of microbial growth in agar plates.

Table 4: Accelerated stability study of D7

Parameters	Time periods			
	Initial one day	One month	Two month	Three month
Assay %	100.42	99.85	99.35	99.23
Viscosity	335.54	334.25	333.52	334.54
pH	7.8	7.7	7.7	7.65
Sedimentation volume	0.97	0.96	0.96	0.95
Redispersibility	+++	+++	+++	+++
Taste	Palatable	Palatable	Palatable	Palatable

4. CONCLUSION

Use of weak cation exchange resin offers superior method for preparing taste-masked substrates of Dicyclomine HCl. A result obtained in this work shows that drug-resin complexes effectively masked bitter taste of Dicyclomine HCl. While liquid formulation provides easier way to administer and getting the child to swallow. Also to overcome problem with non compliance with child especially around 8 years old for whom swallowing other dosage form can be challenging. Thus, the "patient-friendly dosage form" of bitter drugs, especially for pediatric, geriatric, bedridden, and non

cooperative patients, can be successfully formulated using this technology.

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