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Research Article

TASTE MASKING OF DONEPEZIL HYDROCHLORIDE USING DIFFERENT ION EXCHANGE RESINS- A COMPARATIVE STUDY

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ABSTRACT

Taste mainly depends on the physiology, sensitivity and structure of taste buds. It is an important parameter in administering drugs orally. Bitter taste is a major limitation to patient compliance. Donepezil hydrochloride (DH) is a bitter drug used in Alzheimer's disease. Amongst the many techniques for taste masking, using ion exchange resins has been extensively reported. The technique of forming tasteless complexes with bitter drugs involves selection of most appropriate exchanger and optimization of complexing ratio. The aim of the present work was to select the best cationic exchanger amongst Indion 414, Indion 234 and Indion 214. All parameters were optimized to produce drug-loaded tasteless complexes. Complexation was carried out using batch process prior to which, acid-alkali activation was performed to remove adsorbed impurities from the resin bed surface and hence improve loading efficiency. UV-spectrophotometric method was used to determine percent drug loading. The molecular properties of drug resin complexes were studied using Fourier Transform Infra-red Spectroscopy, Differential Scanning Calorimetry and X-ray Powder Diffraction which confirmed complexation. Indion 414 was found to give highest drug loading and minimal drug was released from the complex at salivary pH.

Key words: Donepezil HCl, Ion exchange resins, Molecular properties, Taste masking

INTRODUCTION

Taste is an important parameter in administering drugs orally. The mechanisms of masking taste include adding taste correcting substances such as flavors to confuse the cerebral taste; preventing drug release in mouth and segregating the contact between drug and taste buds; anesthetizing the taste cells to enhance the bitterness threshold or preventing bitter taste receptors from combining with bitter drugs. Bitterness in pharmaceuticals plays a critical role in non-compliance, especially in children and elderly patients. Patient non-compliance consequently leads to dose skipping which hampers therapeutic efficacy of the medicament. Masking undesirable taste of medicaments is a formulation challenge (Douroumis, 2011). Use of sugars, amino acids and fruit flavors, saccharin, anethole-β-cyclodextrin complex, hydroxyl-propyl-β-cyclodextrin and aspartame have been reported (Shalini and Shaila, 2010). Complexation with ion-exchange resins is one of the many technologies used for taste masking. Indion resins are a group of cross-linked polyacrylic resins with particle size less than 150μm. They are popularly used as taste masking agents. Ion exchange resins are cross linked water-insoluble polymers carrying ionizable functional groups. Drugs can be loaded into an ion exchange resin by an exchanging reaction, and hence a drug-resin complex (DRC) is formed (Salve, 2011). Taste masking of Memantine, the first and only representative of a new class of Alzheimer drugs is patented using ion exchange resin (Pilgaonkar *et al.,* 2010). Another patent reports taste masking of solifenacin by contacting its solution with a resin to form a resinate. (Harshal *et al*., 2010).

Donepezil Hydrochloride (DH) was chosen for taste masking using Indion group of resins because it is a highly bitter drug which is

prescribed to geriatric patients suffering from Alzheimer's. DH is a reversible inhibitor of the enzyme acetyl cholinesterase and used for the treatment of mild to moderate dementia of the Alzheimer's diseases (www.drugbank). In order to enhance palatability of the product, taste masking is an important formulation parameter to be considered. Orally disintegrating tablets of DH have been prepared using Eudragit EPO, but the technique involves use of spray dryer which is time consuming and burdensome for process optimization (Yan *et al.*, 2010). Therefore, we have taken the advantage of ion exchange resins as taste masking agents which have also been cited in a number of articles (Chandewar *et al.*, 2011). The purpose of present research was to formulate tasteless complexes of DH using Indion 414, Indion 234 and Indion 214 and optimizing parameters to obtain highest drug loading with efficient taste masking within reasonable time. The molecular properties of the drug-resin complexes were evaluated to confirm complexation of DH with resins. The stability of the DRC in salivary pH was also studied to co-relate that no bitter taste is imparted while the complex is within the oral cavity. A comparative study on Indion 414, Indion 234 and Indion 214 was performed to select the resin which gave efficient taste masking and high degree of drug loading.

METHODOLOGY

Materials

DH was procured from Sun Pharma Ltd., Mumbai, Maharashtra, India. Ion exchange resin; Indion 414, Indion 234 and Indion 214 were obtained as a gift samples from Shreya Life Sciences Ltd., Aurangabad, Maharashtra, India. Deionized water was procured from UDCT, Aurangabad, Maharashtra, India. All the reagents and chemical used were analytical grade and were procured from Y.B. Chavan College of Pharmacy, Aurangabad, Maharashtra, India.

Preliminary evaluation of resin

Particle size analysis

The particle size of the resins Indion 414, Indion 234 and Indion 214 was measured using digital camera microscope using Catcam microscope eyepiece digital camera (DCM 35). The resin powder was placed on a glass slide and was analyzed using microscopy. The average diameter of the resin particles was determined.

Activation of ion exchange resins

Indion 414, Indion 214 and Indion 234 were washed with distilled water. The wet resins Indion 414 and Indion 234 were activated with 1 N HCl and 1 N KOH while Indion 214 was activated with 1 N HCl and 1 N NaOH 100 ml followed by washing with distilled water, then dried overnight in hot air oven at 60°C. The dried resins stored in air tight glass vials (Abhijeet Y. *et al.*, 2012).

Effect of resin activation on drug loading

Resin activation affects % drug loading. This was determined by treating the three resins with following media, followed by using these activated resins for loading the drug namely:1) Acid treatment- 1 N HCl; 2) Alkali treatment- 1 N KOH and 1 N NaOH; as well as 3) Acid-alkali treatment- 1 N HCl + 1 N KOH/ 1 N NaOH.

Acid treatment

Indion 414, Indion 234 and Indion 214 (500mg) was accurately weighed and placed on whatman filter paper No.41 in a funnel. Then washed three times with deionized water and then with 1N hydrochloric solution (three times). Finally, the resins were again washed several times with deionized water till the pH of the resins was neutral. The effect of acid treatment on percent drug loading was studied.

Alkali treatment

Indion 414, Indion 234 and Indion 214 (500mg) was accurately weighed and placed on whatman filter paper No.41 in a funnel. Then washed three times with deionized water and then with 1N KOH (Indion 414 and Indion 234) / 1N NaOH (Indion 214) (three times). Finally, the resins were again washed several times with deionized water till the pH of the resins was neutral. The effect of alkali treatment on percent drug loading was studied.

Table I. Effect of resin activation on drug loading

Sr. No.	Treatment	Percentage of drug loading		
		Indion 414	Indion 234	Indion 214
1	Inactivated resin	74.56±0.41	70.36±0.25	68.78±0.40
2	Activated with hydrochloric acid + deionized water	93.59±0.40	91.55±0.29	89.77±0.39
3	Activated with potassium hydroxide/sodium hydroxide + deionized water	93.71±0.25	92.30±0.25	90.7±0.58
4	Activated with hydrochloric acid + potassium hydroxide/sodium hydroxide + deionized water	97.85±0.35	97.45±0.23	96.55±0.38

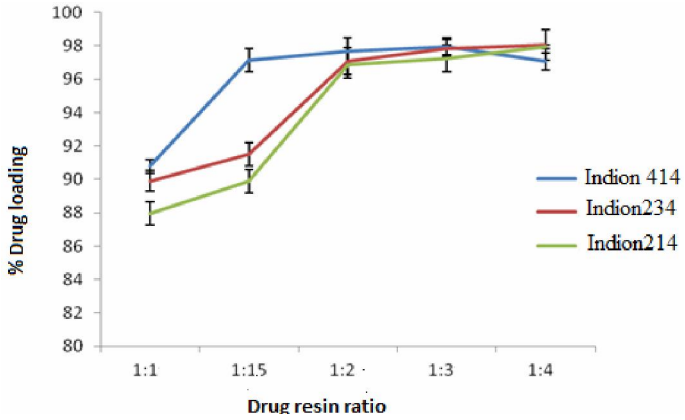

Figure. 1. Optimization of Drug resin ratio (% drug loading),

Acid-alkali treatment

Indion 414, Indion 234 and Indion 214 (500mg) was accurately weighed and placed on whatman filter paper No.41 in a funnel. Then washed three times with deionized water and then with combined treatment of 1N HCl and 1N KOH/1N NaOH solutions (three times). The effects combined acid & alkali treatment on percent drug loading was studied.

Drug loading by formation of DRC and Optimization of Drug resin ratio (DRR)

Initially a 1:1 Drug-resin ratio was selected. Batch process was opted for preparing the DRC. Hundred mg of activated resin was placed in a beaker containing 25mL deionized water. DH (100mg) was added to the resin slurry under magnetic stirring till equilibrium was obtained. On filtration, the residue was washed with 75mL of deionized water. Unbound drug in filtrate was estimated spectrophotometrically at 230 nm. For further studies activated resins were used for optimizing the DRR (Abhijeet *et al.*, 2012).

Different DRR were prepared using activated resins under magnetic stirring. The DRR which gave maximum drug loading was selected for further studies.

Determination of drug threshold bitterness concentration of DH

Six healthy human volunteers held 10mL of aqueous solution of DH of concentration 0, 50, 75, 100, 150, 200 µg/mL respectively, in their mouth for 10 sec followed by rinsing their mouths with 50mL distilled water (Amr *et al.*, 2011). The bitterness threshold concentration was judged by statistical analysis of the volunteers' opinion about taste. A taste scale of 1 to 3 was adopted, with 1= not bitter, 2= bitter and 3=very bitter.

Table II. Effect of swelling of resins on drug loading

Sr. No.	State of Resins	Percentage of drug loading		
		Indion 414	Indion 234	Indion 214
1	Un-swollen resin	79.82±0.51	77.22±0.51	76.22±0.17
2	10 min swelling	87.43±0.54	85.76±0.47	83.76±0.49
3	30 min swelling	97.65±0.32	94.58±0.72	93.48±0.78
4	60 min swelling	97.79±0.35	97.17±0.39	96.99±0.91
5	120 min swelling	97.99±0.47	97.54±0.78	97.19±0.84

Table III. Effect of stirring time on drug loading

Sr. No.	Stirring time (in min)	Percentage of drug loading		
		Indion 414	Indion 234	Indion 214
1	30	97.81±0.21	94.99±0.56	92.57±0.49
2	60	97.89±0.65	96.25±0.97	96.05±0.79
3	120	98.27±0.33	96.42±0.38	96.58±0.67

Optimization of stirring time

Accurately weighed DH (100mg) was added to Beakers containing 150mg Indion 414, 200mg Indion 234 and 200mg Indion 214, dispersed in 25mL deionized water respectively. Four different batches with a stirring time of 10, 30, 60 and 120min. were processed separately. The amount of bound drug was estimated using UV spectrophotometer at 230nm and time required for maximum drug loading was optimized and selected for further studies.

Optimization of swelling time

Activated resins Indion 414, Indion 234, and Indion 214 were soaked in 25mL of deionized water taken in a beaker each for 10, 30, 60 and 120min. separately. The swollen resins were then used for studying the effect on drug loading.

Study of molecular properties of drug-resin complex

The IR spectrum of drug-resin complex was obtained using potassium bromide (KBr) pellet technique. The drug sample was mixed with IR grade KBr and scanned in the range of 4000-400cm^{-1} (Figure 2).

The X-ray powder diffraction patterns of powdered sample of drug-resin complex were recorded using Bruker AXS D8 Advance X-ray diffractometer. Sample was irradiated with monochromatized Cu Kα radiation (1.5406 Aº) and analyzed between 3-70º (2θ). The voltage and current used was 40kV and 30mA respectively (Figure 3).

Thermal behavior of DH and drug-resin complex (DRC) was examined by DSC. Accurately weighed sample of drug-resinate (2.9-4 mg) was run at the scanning rate of 20°C/min over a temperature range of 100 to 250°C. Mettler Toledo Differential Scanning Calorimetry (DSC) 822e equipped with an intra-cooler and a refrigerated cooling system was used to analyze the thermal behavior of DH and DRC. Indium standard was used to calibrate the DSC temperature. Nitrogen was purged at 50mL/min and 100mL/min through cooling unit. The thermal behavior of hermetically sealed samples (10mg) of DH, DRC of Indion 414, DRC of Indion 234 and DRC of Indion 214, heated at 20°C/min is (Figure 4).

Sensory evaluation of taste masked drug-resin complex

A sensory evaluation test was also performed to confirm taste masking. Bitterness of DRC and drug substance was measured by the taste panel of six healthy human volunteers from whom a written consent was obtained. The volunteers were instructed to hold the drug substance and DRC at the centre of the tongue for 30sec and not to swallow.

After the allotted time of 30sec. the volunteers were asked to rinse their mouths thoroughly with water and report the taste (Bhoyar and Amgaonkar, 2011,).

Drug release from drug-resin complex

Drug release from DRC was studied in deionized water and in dissolution media having pH 1.2. All the DRCs were subjected to dissolution studies using United States Pharmacopeia (USP) 24 type II dissolution apparatus. DRC equivalent to 100mg of drug were weighed accurately and added to 900mL deionized water maintained at 37ºC. Drug release study was performed at 50rpm for 120min. Two mL aliquots were removed periodically and analyzed at 230nm for percent drug release (Dahima and Sharma, 2010).

Stability of DRC at salivary pH

The DRCs were added to 10 mL of 6.8 pH buffer. Aliquots were removed at 15, 30 and 60sec. and analyzed at 230nm using a UV spectrophotometer for amount of drug release at salivary pH 6.8.

RESULTS AND DISCUSSION

Batch optimization

Drug resin interaction is an equilibrium phenomenon; maximum drug loading efficacy is achieved in batch process. DH is freely soluble in water and has the desired ionization power for effective complexation. Ion exchange resins are highly porous materials and even though they are water-insoluble, they are capable of hydrating and swelling by absorbing large amounts of water. Particle size of resins affects the hydrating and swelling properties of resins and hence the drug release properties. The particle size of Indion 414, Indion 234 and Indion 214 was found to be 54±2.0, 56.33±1.52 and 65±1.0 µm respectively, which was in conformation with the reported size i.e. less than 150µm. This size range has been reported to be applicable for taste masking and also used as disintegrating agent. Substantially small size particles are difficult to process and particles greater than 200µm have a tendency to fracture.

The effect of activating resins prior to use is summarized in table I, where the percent drug loading with inactivated resin, acid treated, alkali treated and an acid-alkali combined treatments is given.

The acid-alkali activation exposed the exchangeable groups producing rapid drug exchange and hence increasing drug loading capacity. Impurities associated with industrial scale manufacturing or absorbed during storage or handling may be neutralized by treating with combined solutions. Therefore, resins treated with acid-alkali combination were used for further studies.

DRR of 1:1.5 was the optimized batch using Indion 414 as % wt/wt drug loading did not significantly increase on increasing the DRC ratio to 1:3. Whereas, in case of Indion 234, 1:2 and with Indion 214, 1:3 DRR was the optimized batch. A low quantity of Indion 414 was required to give maximum drug loading showing its superior complexation properties over other resins used. Optimization of drug-resin ratio in accordance to % wt/wt drug (Figure 1).

Subjecting the resins to swelling prior to complexation resulted in increase in the drug loading capacity of resin. This phenomenon could be contributed to the increase in exposed surface area of exchanger. Complexation between the drug and resin is essentially a process of diffusion of ions between the resin and surrounding drug solution. In un-swollen resin matrix, the exchangeable groups are latent and coiled toward the backbone, hence not easily approachable for the ionic drug. The effect of swelling time on drug loading (Table II).

A 30min swelling time was optimized to give maximum drug loading as increasing the time to 60min did not give any significant increase in % wt/wt drug loading. The complexes were subjected to stirring using a magnetic stirrer and maximum drug loading was achieved in the batch process due to equilibrium phenomenon between the resins and drug solution. The stirring time optimized was 30min. Further increasing time did not substantially increase drug loading (Table III). The complexation process could be completed in a short time of 30 min., giving an added advantage over other reported methods of taste masking which require more time and stringent conditions.

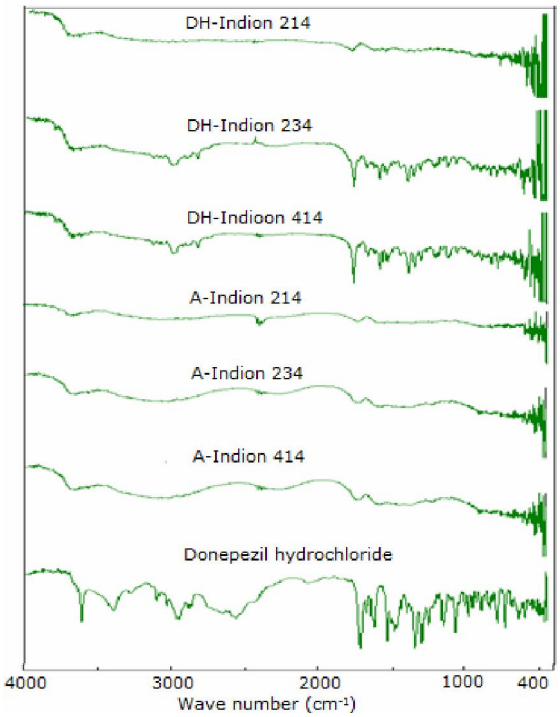

Figure. 2. Infrared spectrum of DH and DRC

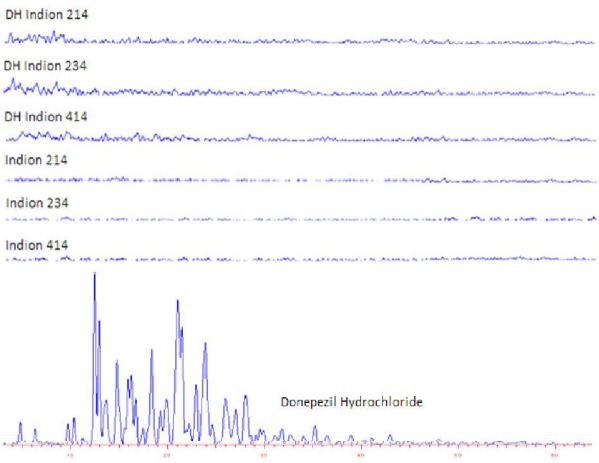

Figure 3. X-ray diffraction patterns

Molecular properties of drug-resin complex

A Fourier transformer infrared (FTIR) spectrum has been used for comparing molecular properties between DH and drug-resin complex. The FTIR study indicates absence of chemical reaction between drug and ion exchange resins during taste masking. In the drug-resin complex, the absence of peaks at 3073cm^{-1} for C-H aromatic stretching signifies that there was complex formation between drug and resins. The piperidine group present in DH did not show any sharp peak, as it is tertiary amine. According to literature review the bitterness of drug has been reported due to presence of C-N group which shows IR peak at 1368cm^{-1}. The FTIR spectra of drug resin complex shows decrease in percentage of

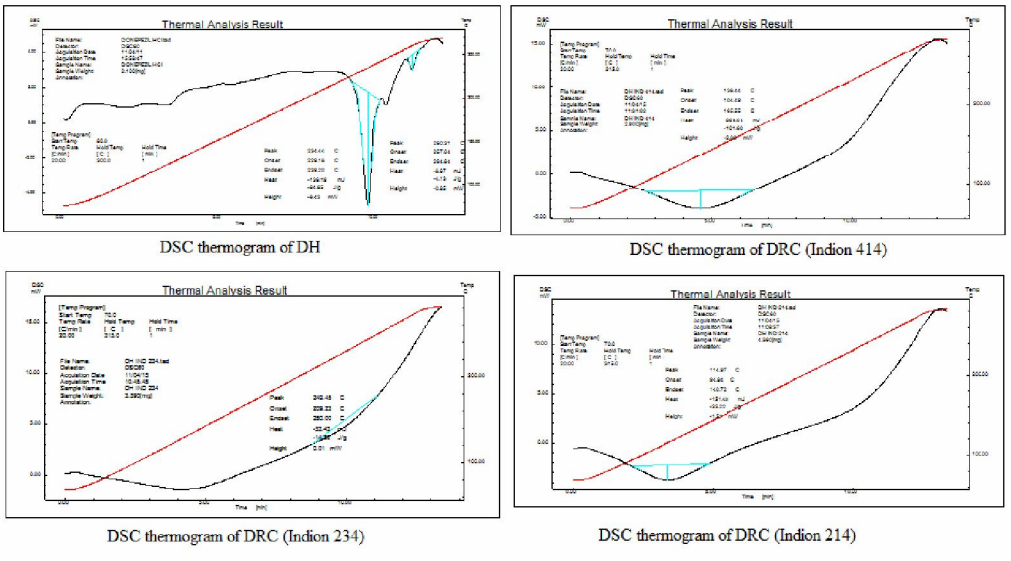

Figure 4. DSC thermogram of DH and DRC

Tab.IV. Determination of Threshold Bitterness Concentration

No. of volunteers	Concentration of drug (µg/mL)				
	50	75	100	150	200
1	1	1	1	2	3
2	1	1	1	2	3
3	1	1	1	2	3
4	1	1	1	2	3
5	1	1	2	2	3
6	1	1	1	2	3

*1= not bitter, 2= bitter, 3= very bitter

intensity of peak as compared to peak observed in FTIR spectra of drug. Thus, the FTIR results confirm formation of DRC which supports taste masking. The FTIR of Indion 414, 234 and 214, DH-resins complex and DH (Figure 2).

X-ray powder diffraction (XRPD) of DH gives evidence of its crystalline state, while the resins are amorphous in nature (Figure 3). The XRPD patterns of DRC purport that the crystalline structure of drug is masked. XRPD pattern of DH show sharp peaks due to presence of crystallinity while resins shows diffused peaks due to their amorphous structure. The prepared DRC shows hollow diffused patterns and the absence of sharp peaks which shows that the drug is mono-molecluarly entrapped in the resin bed. Being amorphous in nature, the drug complexed in resin matrix shows faster dissolution rate due to improved solubility.

Differential scanning calorimetry (DSC) of DH, DRC of Indion 414, 214 and 234.The thermal behavior of DRC shows fractional loss of water at 100-150ºC and absence of endotherms at 233.44ºC (Figure 4).

DSC data supports the XRPD analysis data of the complexes and the observed changes may be due to complex formation and resultant amorphous nature of drug adsorbates. The study confirms the complexation of DH with Indion 414, 214 & 234 and DSC and XRPD results reveal the amorphous nature of drug adsorbates.

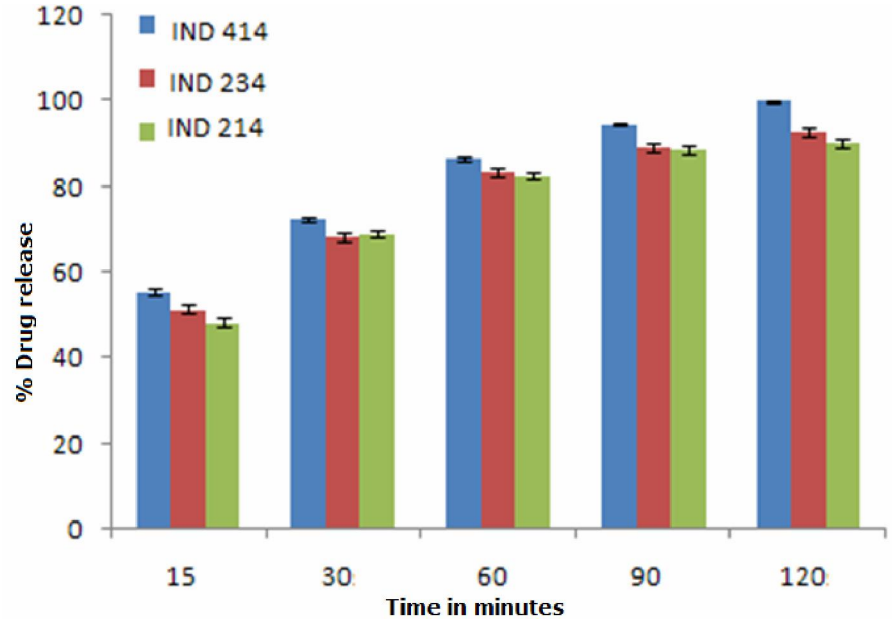

Figure 5. Drug release from DRC in pH 1.2

Evaluation of taste

Taste evaluation in volunteers confirmed that the taste of DH was masked by complexation with Indion 414, 234 and 214. When the drug-resin complexes were subjected to sensory evaluation by human volunteers, the volunteers did not feel any bitter taste after keeping the DRC in mouth for 30 sec, According to study it was found that all the volunteers felt bitterness, after 30 sec of time, for the concentration of 150µg/mL which confirmed that bitter taste of DH was masked successfully.

The release of DH from the drug-resin complex was observed in deionized water for 120 min, in average salivary pH of 6.8 and at gastric pH of 1.2 separately. It was observed that insignificant amount of drug (less than 0.3% wt/wt) was released in deionized water in 120 min, indicating the stability of complexes. Such complexes can in future be formulated as stable suspensions. *In vitro* drug release in salivary pH 6.8 was less than 5% wt/wt within 60sec, which signifies that the DRC is stable in salivary pH during transit of preparation through the oral cavity. The amount of drug released is insufficient to impart bitter taste while the formulation passes through the mouth to further parts of gastrointestinal (GI) tract. At gastric pH of 1.2, DH was completely released in 120min (Figure 5).

CONCLUSION

In conclusion, Drug resin complexes were prepared using a batch process which completed within a considerable short period of 30 min. Drug-resin ratio, swelling time and stirring time significantly affected the batch complexation process. By comparing results obtained using the three resins, it was concluded that Indion 414 gave maximum drug loading efficiency of 97% in a 1:1.5 ratio. This was probably due to its smaller particle size as compared to Indion 234 and Indion 214.

The study of molecular properties using IR, DSC and XRPD provided evidence of complex formation between drug and resin while in taste masking evaluation the volunteers rated the DRC as tasteless and agreeable.

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