Preparation, Characterization, and *In-vitro/vivo* Evaluation of Indion-based Chewable Tablets of Paracetamol and Ibuprofen for Pediatric Use

Amr Helmy[1], Sherien El Kady[2], Ahmed Khames[1, 3]*, Ahmed Abd-elbary[4]

[1]Department of Pharmaceutics, Beni Suief University, Beni Suief, Egypt
[2]E.P.C.I. Company, Beni Suief Gov., Egypt
[3]Department of Pharmaceutics, Taif University, Taif, KSA
[4]Departments of Pharmaceutics, Cairo University, Egypt
dr_akhames@yahoo.com

Abstract: Ibuprofen and paracetamol are commonly used NSAIDs, bitter taste and poor water solubility are great challenges in their formulation. In this work, an attempt was made to prepare palatable chewable tablets of these drugs suitable for pediatric use. In this work; masking of drug bitter taste was adopted using ion exchange technique, drug was loaded onto Indion-204 (a cationic exchange resin). The prepared drug resin complexes were optimized for maximum drug concentration by changing drug: resin ratio, stirring time, swelling time, pH and temperature. Other techniques including coating with Aqua-coat ECD, solid dispersion in HPMC, MC and EC, microencapsulation in EC were also applied. *In-vitro* and *in-vivo* taste evaluation was applied, and the most palatable mixture was selected and formulated into tablets and fully evaluated. The results showed that, Indion-204 had maximum drug loading capacity when activated in acidic (1N HCl) solution, and Drug-Indion-204 tablet mixture prepared at 1: 3 ratio respectively by stirring in neutral solution (pH =7) at 80ºC for 6hrs had a maximum drug loading capacity (85.6 and 90.5% w/w of paracetamol and ibuprofen, respectively), the drug bitter taste was almost completely masked when complexed with Indion. The drug dissolution rate from the prepared tablets reached 99.14% and 98. 48% w/v after 45min for paracetamol and ibuprofen respectively at maximum used drug-resin ratio (1:3). Depending on the previous results; Drug-Indion-204 mixture is an efficient technique to prepare palatable chewable tablets suitable for pediatric use.

[Amr Helmy, Sherien El Kady, Ahmed Khames, Ahmed Abd-elbary **Preparation, Characterization, and *In-vitro/vivo* Evaluation of Indion-based Chewable Tablets of Paracetamol and Ibuprofen for Pediatric Use]** Journal of American Science 2011;7(12):831-844]. (ISSN: 1545-1003). http://www.americanscience.org.

Key words: Paracetamol, Ibuprofen, chewable tablets, ion exchange resin.

1. Introduction

Excessive bitterness of the active principal ingredients in oral formulations is the major taste problem faced by the pharmaceutical industry. Bitterness of formulations can influence selection by physicians and markedly affect patient compliance. Masking of bitter and obnoxious taste of drugs in pediatric and geriatric formulations is a challenge to the pharmacist to ensure patient compliance and product value [(1)].

Two approaches are commonly utilized to overcome bad taste of the drug. The first includes reduction of drug solubility in saliva, where a balance between reduced solubility and bioavailability must be achieved. Another approach is to alter the ability of the drug to interact with taste buds [(2)].

An ideal taste masking process and formulation should be economic, rapid and easy, involve least number of equipments, processing steps and minimum number of excipients without adverse effect on drug bioavailability [(3)].

There are several methods [(4-6)] commonly employed for achieving effective taste masking include use of flavor enhancers, coating of drug particles with inert agents [(7, 8)], formation of inclusion complexes, molecular complexes of drug with other chemicals, complexing with ion exchange resin, microencapsulation [(9)], solid dispersions, multiple emulsions, liposome [(10)], use of insoluble prodrug [(11, 12)], mass extrusion method (dispersion coating), salts or derivatives formation [(13, 14)], use of amino acids and protein hydrolysates, and/or viscosity modifications.

Amongst the numerous available taste-masking methods, ion exchange resins are inexpensive and can be used to develop a simple, rapid and cost-effective method of taste masking [(15)]. Ion exchange resins are water-insoluble, cross-linked polymer containing salt forming groups in repeating position on the polymer chain. These groups have an affinity for oppositely charged counter ions, thus absorbing

the ions into the polymer matrix. Resins charge provides means to loosely bind charged drugs. The binding is generally an equilibrium process, resulting in continuous desorption or elution of drug from the resin as drug is absorbed into the body [8, 16].

Various articles describe the utility of ion exchange resins for taste masking, sustained release, targeted drug delivery, and drug stabilization [17, 18]. The ion exchange resins are available in different size, cross linkage, and functionality making them suitable for various applications. Bitter cationic drugs can get adsorbed on to weak cationic exchange resin of carboxylic acid functionally to form the complex, which is non-bitter [19]. The taste-masking applications of ion exchange resins are reported for various cationic drugs, e.g., ciprofloxacin, chloroquine phosphate [20, 21] .

In Australia, paracetamol and ibuprofen are the most popular over-the-counter drugs used to manage fever and pain in children. Paracetamol and ibuprofen are effective antipyretics and analgesics (ibuprofen is favored in inflammatory conditions) [22- 25]. Oral paracetamol is rapidly absorbed from the small bowel and has an onset of action of approximately 30 minutes and duration of action of four hours [26]. while, oral ibuprofen is rapidly absorbed and has an onset of action of approximately 30 to 90 minutes with duration of action of six to eight hours [27] .

In this work different taste masking techniques will be applied in an attempt to prepare palatable chewable tablets of paracetamol and ibuprofen suitable for pediatric use. *In-vitro* and *in-vivo* taste evaluation studies for the prepared drug mixtures will be applied and compared, and the most palatable mixture will be selected, formulated into tablets and fully evaluated.

2. Materials and Methods

2.1. Materials:

Ibuprofen, Paracetamol and Mannitol were received as gift samples from El-Nasr Pharmaceutical Chemical Co., Abo-Zaabal, Cairo, Egypt. Ethyl Cellulose (EC), Magnesium Stearate, Indion 204, Methyl Cellulose (MC), Avicel PH 101, Povidone K90 and Hydroxypropyl Methyl Cellulose (HPMC) were received as gift samples from EPCI, Bani-Sueif, Egypt. Strawberry Flavor, Orange Flavor and Vanilla Flavor were purchased from Kamena Products Corporation, Giza, Egypt. Aspartame was received as gift samples from Al-Andalous Medical Co., Giza, Egypt. All other ingredients used throughout the study were of analytical grades and were used as received.

2.2. Methods:

2.2.1. Techniques employed for taste masking:

2.2.1.1. Complexation with ion exchange resin:

a. Optimization of drug-resin Complexation:

The drug loading onto the resin was optimized for various processing parameters including activation conditions, swelling time, stirring time, pH, temperature and drug: resin ratio.

1. Effect of activation conditions on resin drug loading capacity:

Indion 204 was washed with distilled water, and subsequently with 1N HCl and 1N NaOH in separate processes for activation. The resin was repeatedly washed with water until neutral pH was reached.

Drug-resin complexes (DRC) were prepared by adding 100 mg of activated resin into beaker containing 50ml distilled water, calculated amount of each drug (100 mg) was added separately onto the beaker to prepare slurry with the aid of magnetic stirrer for three hours at room temperature. On filtration, the residue was washed with 75ml of deionized water. The unbounded drug in filtrate was estimated spectrophotometrically at λ_{max} 243nm and 222nm for paracetamol and ibuprofen respectively, and resin drug-loading capacity after activation on acidic and basic conditions was calculated and recorded.

2. Optimization of resin concentration for maximum drug loading:

For this purpose, different quantities of acid activated resin were placed in different beakers containing adequate quantities of deionized water and allowed to swell for 30 min. Paracetamol and ibuprofen were separately added to each beaker at different ratios (namely; 1:1, 1:2, and 1:3, drug: resin respectively) and stirred using a magnetic stirrer for three hours at room temperature. The mixtures were filtered and residues were washed with adequate quantities of deionized water. The drug-loading efficiency of the resin was estimated as previously mentioned. The ratio of maximum

loading of drug was the optimized ratio.

3. Optimization of stirring time for maximum drug loading:

For this purpose, separate batches of drug-resin complexes at maximum ratio (1:3 respectively) were slurred in adequate quantities of deionized water for 30, 60, 120, 180, 240, 300, 360, and 420 minutes with the aid of magnetic stirrer at room temperature. Resin drug-loading efficiency was estimated as previously mentioned. The time required for maximum drug loading was optimized.

4. Optimization of swelling time of resin for maximum drug loading:

For this purpose, separate batches of acid activated resin were soaked in adequate quantity of deionized water for 10, 20, 30, 40, 50, 60 and 120 minutes at room temperature. To each beaker drug was added at 1:3 drug: resin ratio and mixtures were stirred for 3 hours at room temperature. Resin drug-loading efficiency was estimated as previously mentioned. The swelling time required for maximum drug loading was optimized.

5. Optimization of processing temperature for maximum drug loading:

For this purpose, separate batches of drug-resin complexes at maximum ratio (1:3 respectively) were slurred in adequate quantities of deionized water at different temperatures namely; 25º, 30º, 40º, 50º, 60º, 70º, and 80ºC using temperature-controlled magnetic stirrer for 3 hours. The amount of bounded drug was estimated as previously mentioned.

6. Optimization of pH for maximum drug loading:

For this purpose, separate batches of drug-resin complexes at maximum ratio (1:3 respectively) were slurred in adequate quantities of solutions having pH 1.2, 2, 3, 4, 5, 6, and 7 prepared from standard solutions of hydrochloric acid and sodium hydroxide in a 100-ml beakers, and stirred using a magnetic stirrer for 3 hours at room temperature. The drug-loading efficiency was estimated as previously mentioned.

b. Preparation of drug-resin complexes:

Depending on the results of resin optimization study; batches of drug-indion mixtures at 1:1, 1:2 and 1:3 ratios were prepared as previously discussed at optimized conditions for maximum loading capacity and subjected to further evaluation.

c. Evaluation of the prepared drug-resin complexes:

1. Determination of drug content:

Accurately weighed amounts of the prepared mixtures of paracetamol resinate and ibuprofen resinate equivalent to 10 mg of drug were separately added to 100 ml of 0.1 N HCl and stirred at 100 rpm for 1 h, till the entire drug leached out. The solutions were filtered through a filter paper No. 41 and the drug content was determined spectrophotometrically at λ_{max} 243nm and 222nm for paracetamol and ibuprofen respectively after suitable dilution [28].

2. Determination of drug release rate from the prepared complexes:

Accurately weighed amounts of the prepared complexes equivalent to the normal dose of each drug were subjected to *in vitro* dissolution studies using USP dissolution apparatus II in 900 ml of the suitable dissolution medium (0.1 N HCl for paracetamol and phosphate buffer pH 7.2 for ibuprofen) at 100 rpm and 37±0.5ºC. Aliquots of 5ml were withdrawn at specific predetermined time intervals of 5, 10, 15, 20, 30, and 45 minutes; the amount of the released drug in each sample was determined spectrophotometrically as previously mentioned. The test was carried out by solvent replacement and the calculated amount of released drug was the mean of six determinations.

3. Experimental characterization of the formed exchange complex:

Differential Scanning Calorimetry (DSC):

Samples (2-4mg) of paracetamol, ibuprofen and prepared drug-resinate mixtures for thermal analysis were weighed into an aluminum pan of differential scanning calorimeter (Perkin-Elmer DSC4 U.S.A.), covered with an aluminum lid and crimped into position. The pan was placed in the oven together with a blank (prepared exactly

by the same way but without the sample). The sample and blank were continuously purged with nitrogen gas and thermograms were recorded over a temperature range of (0.0-400ºC) with programmed heating rate of 10°C/min. Temperature calibration was made with an indium standard. The DSC thermograms for the tested samples were recorded and analyzed.

Infrared Spectroscopy (IR):

Samples (2-4mg) of paracetamol, ibuprofen and prepared drug-resinate mixtures were mixed with about 400 mg of dry potassium bromide powder. They were compressed into transparent disc under pressure of 10.000 to15.000 pounds/ square inch; using Infrared spectrophotometer (Shimadzu IR-435, Kyoto, Japan) their IR spectra were recorded and analyzed.

d. Formulation of the prepared drug-resin complexes into chewable tablets:

According to the formulae composition mentioned in table (1), accurately weighed amounts of the prepared complexes of paracetamol resinate and ibuprofen resinate at 1:1, 1:2 and 1:3 drug: resin ratios equivalent to the normal dose of each drug were mixed with other excipients and granulated using 5% w/v ethanolic solution of povidone K90 as granulating solution. The prepared granules were subjected to compression on a rotary tabletting machine; (12 mm diameter concave punch and die set; tablet rotation speed, 30 rpm; punch pressure; 5.0 kp) after lubrication with magnesium stearate.

2.2.1.2. Using solid dispersion:

a. By Fusion method:

Into two separate glass beakers, calculated amounts of hydroxyl-propyl-methyl cellulose and methyl cellulose were added to suitable amounts of paracetamol and ibuprofen to prepare 25% drug mixtures. The mixtures were stirred at high temperature for 1 hour to provide solid dispersions. According to the formulae composition mentioned in table (1), accurately weighed amounts of the prepared solid dispersion equivalent to the normal dose of each drug were mixed with other excipients and tablets were prepared by wet granulation as previously mentioned.

a. By Solvent method:

In this work; drug solid dispersions were prepared in single and binary polymer systems.

Single polymer system:

Into two separate glass beakers, calculated amounts of ethyl cellulose were dissolved in minimum amounts of methylene chloride. Calculated amounts of each drug were separately added to produce 20% drug slurries. The resulting slurries were oven dried until solvent evaporation. The dried films were peeled off and grounded by a porcelain mortar and pestle and passed through 100 µm sieve. According to the formulae composition mentioned in table (1), accurately weighed amounts of the prepared solid dispersion equivalent to the normal dose of each drug were mixed with other excipients and tablets were prepared by wet granulation as previously mentioned.

Binary polymers systems:

Into two separate glass beakers, calculated amounts of hydroxypropyl methyl cellulose, mannitol and methyl cellulose were added. Calculated amounts of each drug were separately dissolved in absolute ethanol and slowly added to each beaker to produce 30% drug slurries. The resulting slurries were mixed well and oven dried till solvent evaporation to provide solid dispersions. The dried films were peeled off and grounded by a porcelain mortar and pestle and passed through 100 µm sieves. According to the formulae composition mentioned in table (1), accurately weighed amounts of the prepared solid dispersion equivalent to the normal dose of each drug were mixed with other excipients and tablets were prepared by wet granulation as previously mentioned.

2.2.1.3. Microencapsulation by coacervation phase separation:

Drug microcapsules were prepared using temperature change to affect phase separation and coacervation as follows; into two separate glass beakers, calculated amounts of ethyl cellulose were dissolved in minimum amounts of cyclohexane. The mixtures were magnetically agitated with two variable speed hot plates. Calculated amounts of each drug were separately added to produce 80% drug slurries. The dispersions were then heated with agitation. The

heat was removed and the temperature was gradually lowered to room temperature over approximately 0.5 to 1 hour with continuous stirring. The prepared microcapsules were allowed to settle and the equilibrium liquid containing the dispersed drug was poured off into a separate container. The batch of microcapsules was then washed twice with fresh cyclohexane, filtered and oven dried till solvent evaporation. The dried films were peeled off and grounded by a porcelain mortar and pestle and passed through 100 µm sieve. According to the formulae composition mentioned in table (1), accurately weighed amounts of the prepared solid dispersion equivalent to the normal dose of each drug were mixed with other excipients and tablets were prepared by wet granulation as previously mentioned.

2.2.1.4. Applying polymer coatings:

In this work; Aqua-coat ECD [30% (w/w) aqueous dispersion of ethyl cellulose (EC) polymer] was applied as a coating polymer for drug as follows. Into two suitable stainless steel plates, each drug was separately wetted by Aqua-coat ECD till slurry was formed then dried at 80ºC. According to the formulae composition mentioned in table (1), tablets were prepared by wet granulation as previously mentioned.

2.2.1.4. Use of sweet and flavor enhancers:

According to the formulae composition mentioned in table (1), the tested drug was geometrically mixed with mannitol and Avicel PH 101. Mixtures were granulated and the dried granules were mixed with suitable sweetener and flavor. Mixtures were subjected to compression using the same mentioned tabletting conditions. In this work; aspartame was used as sweetener and strawberry, orange and vanilla were used as flavors.

2.2.2. Characterization of the prepared formulations:

Angle of repose, Carr's index as well as the Hausner ratio for drug powder and different drug formulation mixtures was determined and compared.

2.2.3. Evaluation of the prepared chewable tablets:

Batches of fifty tablets of paracetamol and ibuprofen different chewable formulae were prepared and fully evaluated by measuring uniformity of tablet thickness and diameter, friability, hardness, and weight variation according to the standardized pharmacopeial conditions of these tests. Also drug content and in-vitro dissolution studies of drug from the prepared tablets were carried out as previously mentioned.

2.2.4. Taste evaluation of the prepared chewable tablets:

Evaluation of taste was done in three parts [1, 28]

a. Assessment of the bitter taste of drug (bitterness threshold):

The bitter taste threshold value of paracetamol and ibuprofen was determined based on the bitter taste recognized by six volunteers. Various concentrations (1-10µg/ml) of each drug were prepared in phosphate buffer pH 6.7. Mouth was rinsed with this solution and then, l0 ml of the most dilute solution was tasted by swirling it in the mouth mainly near the base of the tongue for 30 seconds. If the bitter sensation was no longer felt in the mouth after 30 seconds, the solution was spat out and wait for 1 minute to ascertain whether this is due to delayed sensitivity. Then rinse with safe drinking water. The next highest concentration should not be tasted until at least 10 min have passed. The threshold value was correspondingly selected from the different drug concentrations as the lowest concentration that had a bitter taste.

b. *In-vitro* evaluation of bitter taste of the prepared chewable tablets:

One tablet from each prepared formulae was crushed and placed in 10 ml phosphate buffer pH 6.7 and stirred at 50 rpm. The stirring was stopped at different time intervals such as 0, 30, and 60 seconds, dispersion was filtered, and the concentration of the drug in each filtered formula was estimated spectrophotometrically at 243 nm and 222 nm for paracetamol and ibuprofen respectively. Time for each prepared formula to achieve drug concentration corresponding to threshold bitterness in 10 ml phosphate buffer was recorded.

c. *In-vivo* evaluation of bitter taste of the prepared chewable tablets:

Taste evaluation of the prepared chewable tablets was performed by panel of six volunteers. The pure drug was used as control in this study. The study protocol was explained and written consent was obtained from volunteers. Prepared formulae were chewed in the mouth by each volunteer and the bitterness level was recorded against pure drug using a numerical scale.

Table 1: Formula composition of the prepared chewable tablet mixtures

Component	Formula composition											
	PRC1	PRC2	PRC3	IRC1	IRC2	IRC3	F1	F2	F3	F4	F5	F6
Drug*	-	-	-	-	-	-	+	+	+	+	+	+
DRC (1:1)	288.8	-	-	306.7	-	-	-	-	-	-	-	-
DRC (1:2)	-	298.9	-	-	338.2	-	-	-	-	-	-	-
DRC (1:3)	-	-	373.8	-	-	442	-	-	-	-	-	-
Mg Stearate	4	4	4	4	4	4	4	4	4	4	4	4
Povidone K90	23	23	23	23	23	23	23	23	23	23	23	23
Flavor (1%)	8	8	8	8	8	8	8	8	8	8	8	8
Avicel PH101	30	30	30	30	30	30	30	30	30	30	30	30
Aspartame	20	20	20	20	20	20	20	20	20	20	20	20
EC	-	-	-				-	20	-	20	-	-
MC	-	-	-				200	-	180	-	-	-
HPMC	-	-	-				50	-	60	-	-	-
Aqua-coat	-	-	-				-	-	-	-	18	-
Mannitol	To 770 mg											

Dose: Paracetamol: 80mg, Ibuprofen: 100mg **PCR:** Paracetamol Resinate Complex
IRC: Ibuprofen Resinate Complex **DRC:** Drug Resinate Complex

A numerical scale was used by classifying bitter taste into five levels: level 0: tasteless, level 1: acceptable bitterness, level 2: slight bitterness, level 3: moderately bitterness and level 4: strong bitterness.

3. Results and Discussion:

3. 1. Optimization of drug-resin complexation:

Results of optimization of paracetamol and ibuprofen loading onto the resin for various parameters are shown in tables from (2 to 7)

Results in table (2) show that; the loading capacity of the resin for both drugs was higher when activated in acidic rather than alkaline conditions and this occurs in accordance with cationic nature of the used resin (indion 204) since the COO^- group of the indion is loaded by H^+ of the acid not OH^- of the base [29].

Table 2: Effect of activation conditions on resin drug loading capacity

Activation conditions	% of Drug Bound to Resin*	
	Paracetamol	Ibuprofen
Acidic pH (1 N HCl)	52.35 ± 0.01	63.87 ± 0.07
Alkaline pH (1 N NaOH)	50.19 ± 0.02	61.42 ± 0.09

*Mean ± S.D (n= 3).

Results in table (3) show that the amount of drug loaded onto the resin was higher with increasing polymer concentration; the maximum amount of drug loaded was found to be 82.18±0.07 and 88.27±0.10 in the ratio 1:3 for both paracetamol and ibuprofen respectively. This can be explained by the stoichiometric nature of the exchange reaction between drug and resin in solution. [30]

Table 3: Optimization of resin concentration for maximum drug loading

Drug: Resin Ratio	% of Drug Bound to Resin*	
	Paracetamol	Ibuprofen
1:1	53.42 ± 0.11	61.53 ± 0.09
1:2	78.87 ± 0.09	85.14 ± 0.01
1:3	82.18 ± 0.07	88.27 ± 0.10

*Mean ± S.D (n= 3).

These types of reactions is greatly affected by stirring time as shown in table (4) where the percentage of loaded drug was increased by increasing stirring time. The optimized percentage drug loading (w/w) was found to be 83.14±0.12 and 89.57±0.19 for paracetamol and ibuprofen respectively at maximum used drug-resin ratio (1:3) at a stirring time of 360 min.

Table 4: Optimization of stirring time for maximum drug loading

Stirring Time (minutes)	% of Drug Bound to Resin*	
	Paracetamol	Ibuprofen
30	80.14 ± 0.01	87.23 ± 0.07
60	80.22 ± 0.11	87.58 ± 0.06
120	80.36 ± 0.10	88.14 ± 0.12
180	80.68 ± 0.05	88.59 ± 0.08
240	81.97 ± 0.02	88.67 ± 0.07
300	82.52 ± 0.09	88.92 ± 0.02
360	83.14 ± 0.12	89.57 ± 0.19

*Mean ± S.D (n= 3).

The swelling and hydration properties of resin is significantly affects the rate of the exchange reaction hence loading capacity is increased [31]; this describes the results listed in table (5) where the optimized percentage drug loading (w/w) was found to be 82.07±0.02 and 88.74±0.10 at swelling time of 120 min for paracetamol and ibuprofen respectively at maximum used drug-resin ratio (1:3).

Table 5: Optimization of swelling time of resin for maximum drug loading

Swelling Time (minutes)	% of Drug Bound to Resin*	
	Paracetamol	Ibuprofen
10	79.44 ± 0.02	86.44 ± 0.01
20	79.57 ± 0.05	86.57 ± 0.05
30	80.36 ± 0.11	87.86 ± 0.04
40	80.49 ± 0.08	87.47 ± 0.01
50	81.54 ± 0.09	88.05 ± 0.08
60	81.97 ± 0.05	88.52 ± 0.04
120	82.07 ± 0.02	88.74 ± 0.10

*Mean ± S.D (n= 3).

The temperature effect on the exchange reactions is significant since higher temperatures increases the ion diffusion rate through the exhaustive exchange zone which is markedly shrink by temperature rise [31]. Temperature rise also causes increase in the drug solubility and ionization and this effect directly increases the rate of the exchange reaction especially for poorly soluble and unionizable drugs; the case is magnificent in the used drugs in our study. This can explain the results in table (6); where the optimized percentage drug loading (w/w) was found to be 84.12±0.06 and 89.83±0.07 at 80ºC for paracetamol and ibuprofen respectively at maximum used drug-resin ratio (1:3). It is worthy to say that; uniform drug loading occurs in temperature range of 25-80ºC as higher temperatures can cause significant effects on resin properties.

Table 6: Optimization of processing temperature for maximum drug loading

Temperature (ºC)	% of Drug Bound to Resin*	
	Paracetamol	Ibuprofen
25	82.92 ± 0.01	88.52 ± 0.09
30	83.24 ± 0.12	88.81 ± 0.02
40	83.51 ± 0.13	88.94 ± 0.04
50	83.72 ± 0.09	89.33 ± 0.07
60	83.83 ± 0.03	89.42 ± 0.02
70	83.99 ± 0.12	89.74 ± 0.01
80	84.12 ± 0.06	89.83 ± 0.07

*Mean ± S.D (n= 3).

Drug-resinate complex formation reaction involves exchange of ionized drug molecules and metal ion of the resin; this mode of complexation is affected by pH of the reaction medium. PH conditions that favors ionization of drug and resin cause direct increase in the exchange reaction rate and hence percentage of loaded drug. Results in table (7) show that the percentage drug loaded was increased with pH rise; this is due to the acidic nature of the used resin and drugs where the ionization was favored with pH.

Table 7: Optimization of pH for maximum drug loading

pH	% of Drug Bound to Resin*	
	Paracetamol	Ibuprofen
1.2	79.46 ± 0.07	86.30 ± 0.12
2	79.69 ± 0.01	86.42 ± 0.05
3	80.27 ± 0.10	86.91 ± 0.11
4	80.82 ± 0.08	87.66 ± 0.10
5	82.28 ± 0.02	87.97 ± 0.14
6	82.51 ± 0.07	88.86 ± 0.09
7	83.89 ± 0.09	89.45 ± 0.04

*Mean ± S.D (n= 3).

3. 2. Evaluation of the prepared drug-resin complexes:

The prepared drug-resin complexes were analyzed for their drug contents (Table 8) and were found to be 85.60±0.08 and 90.50±0.09 for

paracetamol and ibuprofen respectively at maximum used drug-resin ratio (1:3). The standard deviation was less than 2 % in all cases. Ion exchange drug resinate complexes have a faster rate of dissolution.

Table 8: Drug content from different prepared drug-resin complexes

Drug: Resin Ratio	Drug Content (%)*	
	Paracetamol	Ibuprofen
1:1	55.40 ± 0.01	65.20 ± 0.06
1:2	80.30 ± 0.13	88.70 ± 0.11
1:3	85.60 ± 0.08	90.50 ± 0.09

*Mean ± S.D (n= 3)

Ion exchange resin matrices are hydrophilic and hence allow water/aqueous solutions to enter the dimensional resin structure, thereby enhancing the dissolution rate. Moreover, each individual drug molecule is bound to a functional site of the resin molecule resulting in reduction of crystal lattice energy, which may be responsible for enhancing the rate of drug dissolution bound to resin [32]. The percentage of drug released was also excellent from the prepared resinate complexes of both drug at all used drug-resin ratios (Figures 1 and 2) the release rate (w/v) reached 99.14% and 98. 48% for paracetamol and ibuprofen respectively at maximum used drug-resin ratio (1:3).

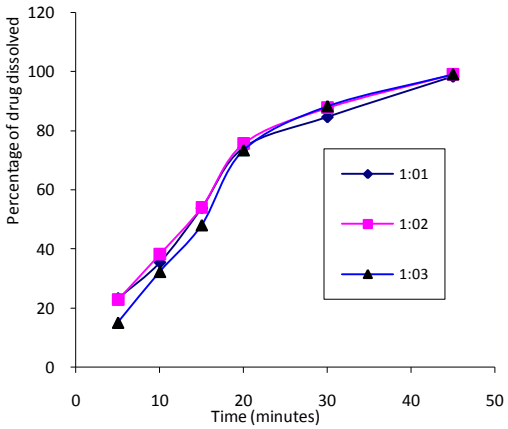

Figure 1: Dissolution profile of paracetamol from the prepared resin complexes at different ratios

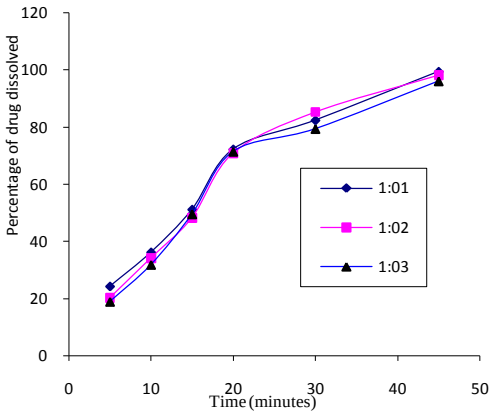

Figure 2: Dissolution profile of Ibuprofen from the prepared resin complexes at different ratios

DSC thermograms of paracetamol and ibuprofen showed sharp characteristic endothermic peaks at 170.18ºC and 76.35ºC respectively (Figures 3 and 4) which was completely disappeared in the thermograms of the drug-resinate mixtures that indicate interaction and complex formation.

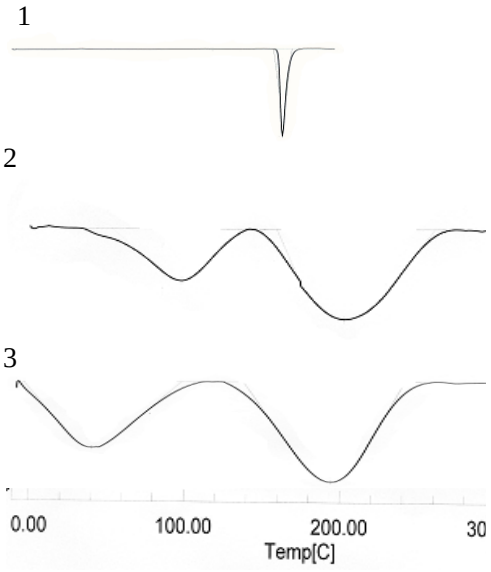

Figure 3: DSC thermograms of (1) Paracetamol, (2) Indion 204 and (3) Paracetamol-resinate complex

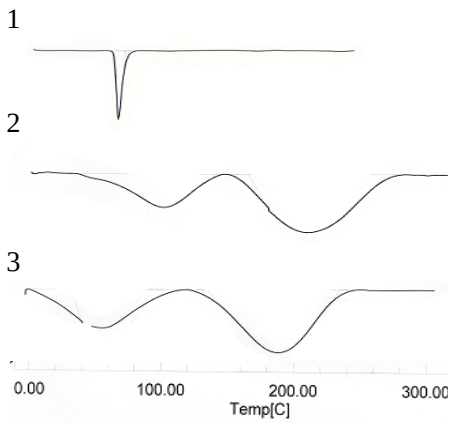

Figure 4: DSC thermograms of (1) Ibuprofen, (2) Indion 204 and (3) Ibuprofen resinate-complex

I.R spectrum of plain paracetamol (Figure 5) showed the main characteristic functional groups as follows: 3324 cm^{-1} (NH), 3160 cm^{-1} (OH), 2929 cm^{-1} (CH aromatic), 1654 cm^{-1} (CO), and 1563 cm^{-1} (C=C aromatic) also ibuprofen I.R spectrum (Figure 6) showed the main characteristic functional groups as follows: 3092 cm^{-1} (CH aromatic), 2955-2870 cm^{-1} (OH acid), 1719 cm^{-1} (CO), 1508 cm^{-1} (C=C aromatic). Figures 5 and 6 also show that; all these groups are clearly observed in drug-resinate spectra of both drugs. This could be due to the low purity of the tested samples hence any traces of non complexed residual drug or resin will show all characteristic peaks in the I.R spectrum.

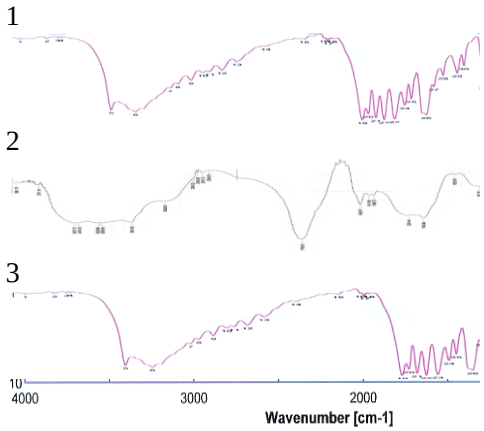

Figure 5: IR spectra of (1) Paracetamol, (2) Indion 204 and (3) Paracetamol-resinate complex

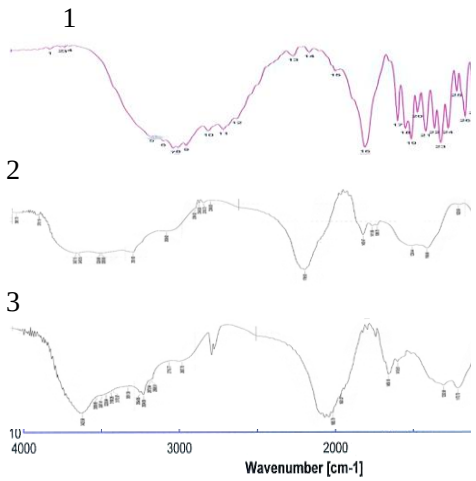

Figure 6: IR spectra of (1) Ibuprofen, (2) Indion 204 and (3) Ibuprofen resinate-complex

Physical properties and characterization of paracetamol and ibuprofen chewable tablet mixtures prepared by different techniques including resinate complexation were evaluated for angle of repose, bulk density, tapped density, Carr's index and Hausner ratio (Tables 9 and 10).
Figure 6: IR spectra of (1) Ibuprofen, (2) Indion 204 and (3) Ibuprofen resinate-complex

All parameters were satisfactory within acceptable limits with hausner ratios close to unity, low Carr's indices and angles of repose around 25º indicating that all the prepared tablet formulae mixtures were of good flow.

Results in Tables 11 and 12 shows that; the prepared chewable tablets of both drugs had uniform thickness and diameter. The values of tablet thickness were in the range of 5.95 to 6.05 mm and the diameter in the range of 12.00 to 12.08 mm. The percentage weight loss was less than 1% in all prepared formulations, insuring good mechanical stability. Hardness values were not less than 50 Newton with standard deviation less than 2% in all formulations; this insures good handling characteristics and mechanical strength. Concerning content uniformity, all the prepared chewable tablets analyzed for their drug contents were found to lie within the official acceptable range (not less than 90% and not more than 110% of the labeled drug dose with standard deviation less than 2%).

Dissolution data of paracetamol and ibuprofen from the prepared chewable tablets formulae were graphically illustrated in Figures (7 to 10). More than 80% of the drug released after 45 minutes from all prepared formulations.

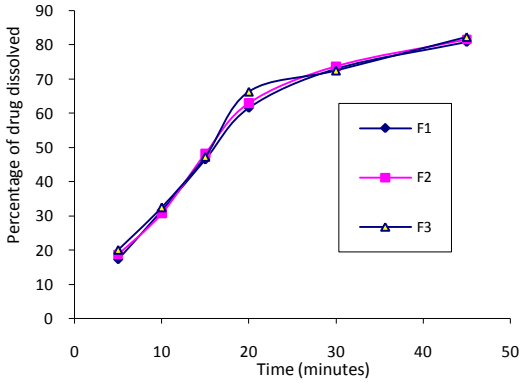

Figure 7: Dissolution profile of paracetamol from prepared chewable tablet formulae

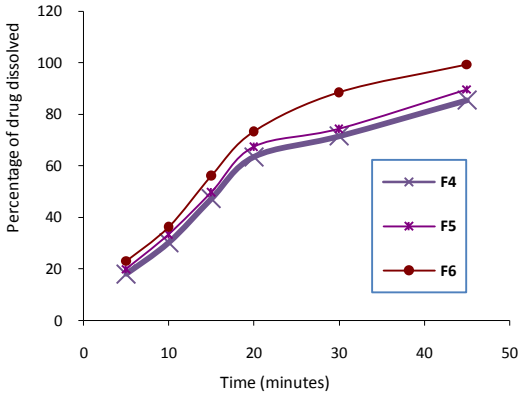

Figure 8: Dissolution profile of Paracetamol from prepared chewable tablet formulae

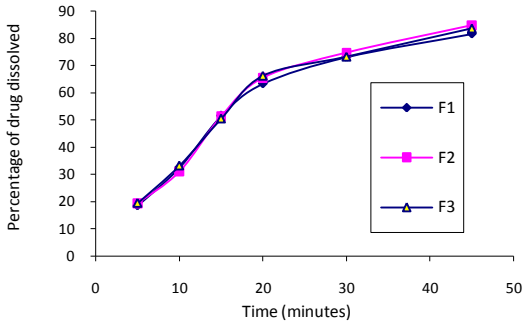

Figure 9: Dissolution profile of Ibuprofen from prepared chewable tablet formulae

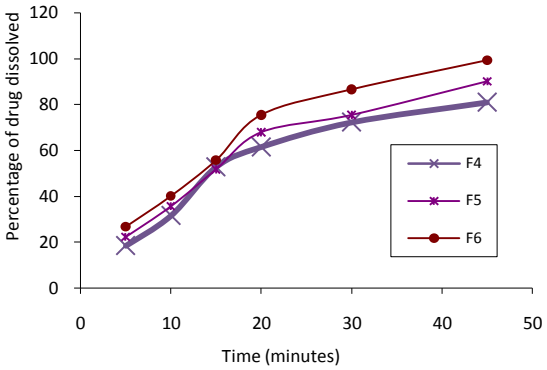

Figure 10: Dissolution profile of Ibuprofen from prepared chewable tablet formulae

3. 3. Taste evaluation of the prepared chewable tablets:

Most volunteers reported the threshold bitterness concentration at 5µg/ml and 4µg/ml for paracetamol and ibuprofen respectively (Table 13). Time for attainment of this threshold bitterness concentration for both drugs is shown in Table 14. It is right clear that, drug resinate complex based formulae prepared at maximum resin concentration (1:3) of both drugs had the lowest concentration after 60 seconds and the time for the determined threshold bitterness concentration to be achieved in buffer of salivary pH showed that the two drugs are not released in saliva to attain threshold bitterness concentrations thereby masking the bitter taste satisfactorily.

This was ascertained by results of the in-vivo evaluation study (Table 15); where the drug resinate complex based formulae prepared at different resin concentrations for both drugs recorded the lowest bitterness level against pure drug on the proposed numerical scale, indicating the most acceptable chewable tablets in their taste.

Table 9: Physical characteristics of paracetamol powder and different drug formulations

Formula No.	Angle of repose	Initial volume (cm^3)	Tapped volume (cm^3)	Carr's index (C_i %)	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Hausner ratio
Drug Powder	33.39	7.0	5.8	17.16	0.714	0.862	1.20
F1	27.02	7.2	6.1	15.26	0.694	0.819	1.18
F2	28.17	7.2	6.0	16.68	0.694	0.833	1.20
F3	26.58	7.1	5.9	16.88	0.704	0.847	1.20
F4	22.93	7.5	6.4	14.72	0.666	0.781	1.17
F5	26.67	7.2	6.1	15.26	0.694	0.819	1.18
F6	27.32	7.1	6.2	12.65	0.704	0.806	1.14
PRC1	26.86	7.2	6.1	15.26	0.694	0.819	1.18
PRC2	23.57	7.6	6.3	17.15	0.657	0.793	1.20
PRC3	26.14	7.7	6.5	15.60	0.649	0.769	1.18

Table 10: Physical characteristics of ibuprofen powder and different drug formulations

Formula No.	Angle of repose	Initial volume (cm^3)	Tapped volume (cm^3)	Carr's index (C_i %)	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Hausner ratio
Drug Powder	34.92	7.1	6.2	12.65	0.704	0.806	1.14
F1	26.20	7.3	6.4	12.41	0.684	0.781	1.14
F2	24.41	7.1	6.0	15.48	0.704	0.833	1.18
F3	29.53	7.1	6.2	12.65	0.704	0.806	1.14
F4	27.82	7.2	6.1	15.26	0.694	0.819	1.18
F5	27.93	6.9	5.8	16.00	0.724	0.862	1.19
F6	26.75	7.2	6.3	12.48	0.694	0.793	1.14
IRC1	22.61	6.9	5.9	14.52	0.724	0.847	1.16
IRC2	24.44	7.1	6.0	15.48	0.704	0.833	1.18
IRC3	24.92	7.3	6.4	12.41	0.684	0.781	1.14

Table 11: Evaluation of the prepared paracetamol chewable tablets

Formula No.	Mean Weight (mg)±S.D.	Mean Thickness (mm)	Mean Diameter (mm)	Mean Hardness (N)±S.D.	Friability (%)	Content Uniformity (%)±S.D.
F1	773.6±0.18	6.00±0.08	12.01±0.32	63.2±0.14	0.235	100.71±0.04
F2	770.9±0.24	6.01±0.12	12.02±0.21	68.9±0.21	0.214	101.90±0.05
F3	774.4±0.07	6.02±0.09	12.05±0.13	79.4±0.41	0.205	101.21±0.01
F4	778.2±0.09	5.95±0.14	12.01±0.01	81.4±0.07	0.197	99.50±0.15
F5	777.1±0.13	6.05±0.03	12.01±0.15	72.3±0.07	0.133	99.62±0.14
F6	775.0±0.24	6.01±0.11	12.07±0.05	78.0±0.13	0.104	100.51±0.09
PRC1	777.8±0.12	6.05±0.12	12.04±0.08	88.7±0.05	0.123	98.63±0.08
PRC2	775.4±0.06	6.04±0.05	12.08±0.01	88.5±0.01	0.109	99.42±0.04
PRC3	772.3±0.14	6.01±0.01	12.02±0.04	90.4±0.07	0.121	100.84±0.09

Table 12: Evaluation of the prepared ibuprofen chewable tablet

Formula No.	Mean Weight (mg)±S.D.	Mean Thickness (mm)	Mean Diameter (mm)	Mean Hardness (N)±S.D.	Friability (%)	Content Uniformity (%)±S.D.
F1	771.2±0.08	6.01±0.14	12.00±0.20	78.4±0.07	0.369	100.99±0.13
F2	769.5±0.02	6.02±0.05	12.01±0.10	81.3±0.04	0.487	98.21±0.17
F3	768.2±0.12	6.00±0.08	12.02±0.02	82.7±0.24	0.108	102.80±0.09
F4	774.0±0.07	5.99±0.26	12.08±0.11	85.0±0.09	0.127	98.87±0.24
F5	774.2±0.04	6.01±0.04	12.00±0.09	79.5±0.13	0.299	98.77±0.05
F6	779.7±0.08	6.02±0.01	12.06±0.08	81.2±0.04	0.234	103.42±0.14
IRC1	773.7±0.05	6.01±0.07	12.02±0.07	91.5±0.18	0.209	99.55±0.05
IRC2	778.4±0.11	6.05±0.13	12.01±0.06	89.3±0.24	0.235	100.14±0.18
IRC3	771.5±0.23	6.02±0.05	12.01±0.03	88.2±0.11	0.144	101.13±0.14

Table 13: Determination of drug threshold bitterness concentration

Volunteer No.	**Threshold Bitterness Concentration (mg/ml)**	
	Paracetamol	**Ibuprofen**
1	5	4
2	4	4
3	5	4
4	5	4
5	5	5
6	5	4

Table 14: Time for attainment of threshold bitterness concentration of the prepared chewable tablets

Formula No.	**Paracetamol**				**Formula No.**	**Ibuprofen**			
	Stirring Time (seconds)					**Stirring Time (seconds)**			
	Concentration (mg/ml)	**0**	**30**	**60**		**Concentration (mg/ml)**	**0**	**30**	**60**
F1		6.15	6.34	7.10	**F1**		7.69	8.69	9.42
F2		6.14	7.55	7.69	**F2**		7.47	8.12	8.34
F3		5.74	7.35	7.95	**F3**		7.94	8.66	9.32
F4		5.25	5.63	6.87	**F4**		6.89	8.69	9.12
F5		6.35	7.64	7.78	**F5**		6.87	8.57	9.64
F6		5.96	6.97	7.63	**F6**		7.63	8.47	9.88
PRC1		5.43	5.97	6.02	**IRC1**		6.31	6.97	7.23
PRC2		4.29	4.87	5.12	**IRC2**		5.48	5.77	6.32
PRC3		3.21	3.62	3.98	**IRC3**		3.01	3.62	3.78

Table 15: Bitterness evaluation the prepared chewable tablets by taste panel

Formula No.	Paracetamol						Formula No.	Ibuprofen					
	Volunteer No.							Volunteer No.					
	1	2	3	4	5	6		1	2	3	4	5	6
Pure Drug	4	4	4	4	4	4	Pure Drug	4	4	4	4	4	4
F1	2	2	3	3	2	4	F1	3	2	2	3	4	4
F2	4	3	3	2	3	4	F2	2	4	3	3	4	4
F3	3	4	4	3	4	3	F3	3	3	4	3	3	4
F4	3	2	2	3	3	2	F4	2	3	3	2	1	2
F5	4	4	2	4	3	4	F5	4	3	4	4	2	4
F6	4	4	4	4	4	3	F6	4	3	4	4	3	4
PRC1	2	1	1	1	2	2	IRC1	1	0	2	1	1	2
PRC2	0	2	1	1	0	1	IRC2	1	1	0	1	1	0
PRC3	0	0	0	1	1	0	IRC3	0	1	0	0	0	1

4. Conclusion:

The results of this study proved that ion exchange complexation with indion 204 resins could efficiently mask Paracetamol and Ibuprofen bitter taste when compared with the commonly used taste masking techniques. The prepared tablets showed excellent results regarding powder flow and tabletting properties. So we recommend this technique for preparation of chewable tablets of palatable taste suitable for pediatric use.

Corresponding author
Ahmed Khames
[1]Department of Pharmaceutics, Beni Suief University, Beni Suief, Egypt
[2]E.P.C.I. Company, Beni Suief Gov., Egypt
dr_akhames@yahoo.com

References:

1. Sohi H, Sultana Y, Khar R.K. (2004). Taste masking technologies in oral pharmaceuticals: recent developments and approaches. Drug Dev Ind Pharm.; 30: 429-448.
2. Brahmankar DM, Jaiswal SB (1995). Biopharmaceutics & Pharmaceutics. 1st Ed. 1995: pp 335,162-163,165.
3. Borodkin S, Yunker MH (1970). Interaction of amine drugs with a polycarboxylic acid ion-exchange resin. J Pharm. Sci.; 59:481-6.
4. Kuchekar BS, Badhan AC, Mahajan HS (2003). A Novel Drug Delivery System. Pharma Times.; 5: 403-28.
5. Mendes RW, Anaebonam AO (1990). Chewable Tablet. In: Encyclopedia of Pharmaceutical Technology, Volume 2, Swarbrick J, Boylan JC, ed. Marcel Dekker, Inc., New York, , p. 397.
6. Tsau. "U.S. Patent" 1994, No. 5286489.
7. Goldburg AH, Skar AA. "U.S. Patent" 2000, No. 6268368.
8. Borodkin S, Sundberg DP (1971). Polycarboxylic acid ion-exchange resin adsorbates for taste coverage in chewable tablets. J Pharm. Sci.; 60(10):1523-7.
9. Agarwal R, Mittal R, Singh A (2000). Studies of ion-exchange resin complex of chloroquine phosphate. Drug Develop. Ind. Pharm., 26,773.
10. Deasy BP (1984). In: Microencapsulation and related processes. Marcel Dekker, New York, , pp. 245.
11. Bakan IA, Lachman L, Liberman, HA, Kanig, JL (1991). In: The theory and practice of Industrial Pharmacy. 3rd ed. Marcel Dekker, Bombay, pp. 413.
12. Eby GA. "U.S. Patent" 1992, No. 5095035.
13. Morozowich W, Sinkula AA, Rowe EL. (1973) Chemical modification of clindamycin: synthesis and evaluation of selected esters J. Pharm. Sci., 62(7): 1106-11.
14. Kuchekar BS, Badhan AC, Mahajan HS (2003). *Mouth Dissolving Tablets: A Novel Drug Delivery System*. Pharma Times., 35:7-9.
15. Roy G (1997). General ingredient or process approaches to bitterness inhibition and reduction in oral pharmaceuticals. In: Roy G, editor. Modifying Bitterness: Mechanisms, Ingredients and Applications. Lancaster, P.A.: Technomic Publishing;. p. 285-320.
16. Borodkin S, Yunker MH (1970). Interaction of amine drugs with a polycarboxylic acid ion-exchange resin. J Pharm. Sci., 59:481-6.

17. Devi V, Krishna M (2001). Advances in controlled and novel drug delivery. In: Jain NK, editor. 1st Ed.; CBS publishers and Distributors. pp. 290–306.
18. Anand V, Kandarapu R., Garg S (2001). Ion-exchange resins: Carrying drug delivery forward. Drug Discov. Today, 6:905–14.
19. Borodkin S (1991). Ion exchange resins delivery systems. In: Tarcha PJ, editor. Polymers for Drug Delivery. 1st ed.; Florida: CRC Press, Inc. pp. 215–30.
20. Pisal S, Zainuddin R, Nalawade P, Kadam MK (2004). Molecular properties of ciprofloxacin-Indion 234 complex. AAPS Pharm Sci Tech., 5(4):e62 15760059 Cit: 3 Available from: http://www.aaps pharmscitech.org.
21. Goldman RD, Ko K, Linnett LJ, Scolnik D (2004). Antipyretic efficacy and safety of ibuprofen and acetaminophen in children. Ann. Pharmacother., 38: 146-50.
22. Perrott DA, Piira T, Goodenough B, Champion GD (2004). Efficacy and safety of acetaminophen vs. ibuprofen for treating children's pain or fever, a meta-analysis. Arch. Pediatr. Adolesc. Med., 158: 521-6.
23. Wahba H (2004). The antipyretic effect of ibuprofen and acetaminophen in children. Pharmacotherapy, 24: 280-4.
24. Beggs S (2008). Paediatric analgesia. Aust. Prescr., 31: 63-5.
25. Sweetman SC (2005). Editor. Martindale: the complete drug reference. 34th Ed. London: Pharmaceutical Press.
26. Kirchheiner J, Brockmöller J (2005). Clinical consequences of cytochrome P450 2C9 polymorphisms. Clin. Pharmacol. Ther. 77: 1-16.
27. Chaudhari PD, Chaudhari SP, Lanke SD, Patel N (2007). Formulation and *in vitro* evaluation of taste masked orodispersible dosage form of levocetrizine dihydrochloride. Ind. J Pharm. Educ. Res., 41:319-27.
28. Avari NG, Bhalekar M (2004). Cation exchange resins for taste masking and rapid dissolution of sparfloxacin. Indian Drugs, 41(1): 19-23.
29. Inderbir singh Ashish K. rehni, Rohit kalra, Gaurav Joshi, Manoj kumar, Hassan Y. aboul-enein (2007). Ion Exchange Resins: Drug Delivery and Therapeutic Applications. FABAD J. Pharm. Sci., 32: 91-100.
30. Dorfner K (1972). Ion exchanger properties and applications 3rd ed. Vol. 2. Ann Arbor Science Publisher, pp. 44–54.
31. Dahima R, Sharma R (2010). Comparative study of ion-exchange resin Indion 204 and Indion 214 for the taste masking of metoclopramide hydrochloride and formulation of rapid-disintegrating tablets. Asian J Pharm., 4: pp.110-5.
32. Hughes L. New uses of ion exchange resins in pharmaceutical formulations. www.rohmhaas.com.

12/12/2011