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Development of Taste Masked Oral Suspension of Mefenamic Acid and Paracetamol for Increase Acceptability.

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ABSTRACT

Formulation and characterization of taste masked oral suspension of Mefenamic acid and Paracetamol by ion exchange resin method. The pediatric Population are most sensitive for the bad taste of medicaments. And pediatric are also unable to take tablets and capsule easily. So, taste mask suspension play an important role in the pediatric health. Because it is liquid form to take by children's in easily manner. In the present work, aimed to prepare taste masked oral suspension of Mefenamic acid and Paracetamol. In this formulation, itwas observed that bitter taste of suspension due to the Mefenamic acid drug. So, object was mask the taste by complexation ofMefenamic acid and ion exchange resin (IER) polymers. In this method, Seven formulations were developed by using two different types of ion exchange resin polymers Kyron T-134 and Doshion 544P in different ratio such as (1:1, 1:2, 1:3) respectively.. Here formulation F1 use as a reference formulation because it's not contain any ion exchange resin polymer. F2-F4 were prepare by Kyron T-134 and formulation. F5-F7 were prepare by Doshion 544P. Hence, in the final results, F7 gives the % drug release and assay were (99.98, 99.95) and (99.989, 99.980) of Mefenamic acid and Paracetamol. That's by F7 Formulation was acceptable and other all physical and chemical parameters alsosatisfactory.

Keywords: Taste masking Suspension, Mefenamic Acid, Paracetamol, Ion exchange Resin (IER), Doshion-544 P, KyronT-134.

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INTRODUCTION

The formulations of tablets and capsules are unsuitable for when administering high doses of Active Pharmaceutical Ingredient (API) since individual large dose is difficult to swallow, or require the administration of several tablets or capsules at a time, making it less patient compliant [1]. Also chewable tablets are also not ideal with pediatric and geriatric patients due to need of chewing, poor taste masking and lack of control release possibility [2]. So Children are frequently failed to take medications properly because of unpleasant taste of medicament. So Non-compliance can lead to worsening of diseased condition [3]. The oldest phenomena was "The worse the taste of the medication, the better the cure". But today a change in patient attitude and development of taste masking technique has reversed this oldest opinion. Patients now expect and demand formulations that are pleasantly, or at least tolerably flavoured [9]. Oral liquid suspensions are majorly designed for the patients with difficulty in swallowing because most of the drugs (API) are bitter in nature [6]. The making of Pharmaceutical suspension is major need in poorly soluble drugs, which are not dissolve complete in systems, its help to take medications.A pharmaceutical suspension isa course dispersion in which insoluble solid particles are dispersed in a liquid medium. The most part of particles have greater than 0.1 micron diameter and some of the particles are observed under the microscope to exhibit Brownian movement if the suspension has a low viscosity. [6]For the betterpatient compliance different taste masking technologies have been used. Various sweeteners, amino acids and flavoring agents used in Conventional taste masking techniques for masking the taste of highly bitter drugs. [1]For taste masking, complexation with Ion exchange resin (IER) provides alternative method [2]. When making the drug resin complex, it gives absolutely tasteless and not affect bioavailability of drug [7]. Ion exchange resins (IERs) have high molecular weight polymers with cationic and anionic functional groups (most common polymeric network is a copolymer of styrene and di-vinylbenzene)[1]. By either repeated exposure of the resin to the drug in a chromate graphic column or by prolonged contact of resin with the drug solution,Drug can be bound to the resin.Formation of insoluble adsorbates or resinates through weak ionic bonding whendrugs are attached to the oppositely charged resin substrate, so that dissociation of the drugresin complex does not occur under the salivary pH conditions [4]. Drugrelease from the resin depends on the properties of the resin and the ionic environment within the GIT. By exchanging with appropriately charged ions in the GIT,Drug molecules attached to the resin are released, followed by diffusion of free drug molecule out of the resins [1]. Paracetamol and Mefenamic acid is a orally absorbed drugs, Paracetamol and Mefenamic acid are both comes in NSAIDs category and both are anti-pyretics and anti-inflammatory , Paracetamol used in treating fever, Muscle pain, Pain, Sciatica, and Mefenamic acid used in treating Pain Period Pain (Dysmenorrha),migraine headache, tooth Pain, Muscles and joint Pain, Rheumatoid Arthritis [19].

MATERIALS AND METHODS

Materials

Paracetamol and Mefenamic acid was gifted fromAkums drug pharmaceuticals Ltd., (Hardwar, U.K India). Kyron T-134 was purchased from Corel Pharma Pvt. Ltd (Ahmedabad, Gujarat, India). Doshion-544P was gift from Doshion Ltd. (Ahmedabad, Gujarat, India) and sucralose, sorbitol, xanthan gum, aspartame, methyl paraben and propyl paraben, sodium benzoate,sodium lauryl sulphate,colloidal silicon di-oxide, flavour mango, flavourpeppermint, sunset yellow colour was purchased from S.D fine chemicals (Mumbai,India).All other chemicals/solvents were of analytical grade.

Methodology

Formulation of Taste Masked Suspension of Paracetamol and Mefenamic acid

Step 1: Preparation of drug resin complex

Weighed quantityof resin, Kyron T-134 or Doshion-544P was added in different ratio (1:1, 1:2, 1:3) in clean beaker containing specifiedquantities of water with stirring for 15 m.[7] Now,weighed the quantity of Mefenamic acid was added in this resinsolution and continuously stirred for 4-5 h. For preparation of paracetamol dispersion phase, Paracetamol was added into the sorbitol solution under continuous stirring for 2 h. After stirring,Paracetamol dispersion phase was added into the drug resin complex of the Mefenamic acid.The final liquidwas obtain and used forfurther preparation of suspension. (Table 1)[3]

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Step 2: Preparation of syrup base

A weighed quantity of sucralose and aspartame were dissolved in specific quantity of boiledwater and filtered it. Then, weight specific quantity of sorbitol solution,methyl paraben, propyl paraben,sodium benzoate,sodium lauryl sulfate, colloidal silicon dioxide,xanthan gum,citric acid were added in this filtrateunder continuous stirring and continued for 15 m.(Table 1)[4]

Step 3: Mixing of drug resin complex with Syrup

Table 1: Composition of Paracetamol and Mefenamic Acid Suspension with Different Resins

Ingredient	F1	F2	F3	F4	F5	F6	F7
Preparation of Dispersion Phase or Drug Resin Complex							
Mefenamic Acid	10	10	10	10	10	10	10
Paracetamol	25	25	25	25	25	25	25
Doshino-544P	-				10	20	30
Kyron-T -134	-	10	20	30	-	-	-
Purified Water	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Preparation of Syrup Phase							
Methyl Paraben	1.2	1.2	1.2	1.2	1.2	1.2	1.2
Propyl Paraben	0.200	0.200	0.200	0.200	0.200	0.200	0.200
Aspartame	1	1	1	1	1	1	1
Sucralose	2	2	2	2	2	2	2
Citric Acid	0.150	0.150	0.150	0.150	0.150	0.150	0.150
Sorbitol 70%	400	400	400	400	400	400	400
Sodium lauryl Sulphate	0.206	0.206	0.206	0.206	0.206	0.206	0.206
Sodium Benzoate	3	3	3	3	3	3	3
Colloidal Silicon Dioxide	2	2	2	2	2	2	2
Xanthan Gum	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Purified Water	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Preparation of Final Suspension and Final Volume							
Sunset Yellow	0.020	0.020	0.020	0.020	0.020	0.020	0.020
Mango RSV	1	1	1	1	1	1	1
Peppermint	2	2	2	2	2	2	2
Purified Water	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Total	**1000**	**1000**	**1000 ml**	**1000 ml**	**1000 ml**	**1000 ml**	**1000 ml**

(All ingredients are in g)

Maintain the temperature of drug resincomplex and syrup basebelowat 40 ^{0}C.Drug resin complex was added in to the syrup base continues under stirring and maintain the temperature at 40-50^{0}C. Now, weighed quantities of coloring agent sunset yellow &flavoring agentsmango and peppermint were added in above solution & stirred for 10 m.Flavoring Agents are carefully added because flavors is volatile in nature. So, minimum temperature of bulk kept maintain due to evaporation of flavoring agent at high temperature. Now

temperature of bulk preparation was recorded.The volume of suspension was make up with the required quantity of purified water.(Table 1)[4]

Evaluation parameters

Appearance of suspension

Various formulations batch (F1-F7) were inspected visually for their appearance.

Taste characterization

Taste was evaluated by humanvolunteers. The study protocol and result consent was explained and obtained from volunteers. Suspension (equivalent to 50 mg) of Mefenamic acid and Paracetamol were held in the mouth for 15s by each volunteer. The bitterness level was compared with formulation F1 [7].

Particle size measurement

Optical microscopy was carried out to study the size of suspended particles. The mean particle size was calculated by measuring the size of 200 particles with the help of calibrated ocular micrometer [7,5].

Determination of Viscosity

The help of a brook field viscometer DV-I prime spindle no.LV-3 (63)was used to measure the viscosity with the speed of 60 rpm, and temperature at 25^0C. 15 ml ofsuspension has taken in 25ml of glass beaker and the viscometer is set over the beaker by a stand such a way that its bob is completely immersed in the suspension. Switch on the viscometer and run it till its indicator is shifted from red zone to green zone. [7]

pH

pH of the suspension was determined by the use of pH meter. Firstly 30 ml of sample was take in a 50 ml clean and dry test tube. After that, pH electrode was dispersed in test tube and shake gently observed pH after 5 m [4,3].

Weight per ml

Weight per ml was measured by thoroughly clean and dry calibrated pycnometer. Fill the pycnometer with the product, adjust the temperature of the filled pycnometer and take weight of filled pycnometer. Determine the weight milliliter by dividing the weight in air, in gm, of the quality of liquid which filled the pycnometer of the specified temperature,by the capacity expressed in ml,The factor is 0.997 at 25 ^{0}C.

Redispersibility

The redispersibility was calculated by placing suspensions 50 ml in measuring cylinder and stored for 10 days. The measuring cylinder was tilted to 90^o until the sediment dispersed uniformly.Suspensions without flocculating agent had poor redispersibility while suspensions having flocculating agent eg. (Potassium chloride) had good redispersibility. However the time required for complete dispersion was recorded [7].

Sedimentation volume

The formulated suspensions were evaluated for physical stability by determining the sedimentation Volume. Each of suspension was taken in 50 ml stopped graduated measuring cylinder. The suspension was dispersed thoroughly by moving upside down for three times. Later, the suspension was allowed to settle for three minutes and the volume of sediment wasn oted. This is the original volume of sediment (H0).The cylinder was kept undisturbed for 14days. The volume of sediment read at 1 h and on the 14th daywas considered as final volume of sediment (Hu). There dispersability of the suspensions was checked by moving the stoppered cylinder upside down until there was no sediment at the bottom of the cylinder.[4,13]

Volume of sedimentation (F) = Ho/Hu

***In-vitro* drug release profile of Paracetamol**

In vitro drug release of the suspension was carried out using USP– type II dissolution apparatus (paddle type).Firstly, dissolution medium of 500 ml of 0.1N HCL was placed in to the vessels of dissolution apparatus and maintain the temperature at 37 ± 0.5 ^{o}C and rpm at 25. Now, 5 ml suspension was pipette in each vessels. Withdrawn the samples of 10 ml in every 5 min intervals and pipette in the fresh medium at the same time. After withdrawing, the samples was filter out by using 0.45 µm filter paper. Collect the samples and diluted with 0.1N HCL and analyzed in UV at 249 nm.[14,15]

***In-vitro* drug release profile of Mefenamic acid**

In vitro drug release of the suspension was carried out using USP – type II dissolution apparatus (paddle type).Firstly, dissolution medium of 900 ml of 0.1N HCL was placed in to the vessels of dissolution apparatus and maintain the temperature at 37±0.5 ^{o}C and rpm at 50.The apparatus was allowed to run for 60 minutes. Now, 10 ml suspension was pipette in each vessels. Withdrawn the samples of 10 ml in every 5 min intervals and pipette in the fresh medium at the same time. After withdrawing, the samples was filter out by using 0.45µm filter paper. Collect the samples and diluted with 0.1N HCL and analyzed in UV at 279 nm.[16-21]

Assay of Suspension

Take 10 ml of suspension was taken in 100 ml volumetric flask & volume was make up with mobile phase (Buffer + acetonitrile)up to 100 ml and sonicate for 15 minutes for the completely dissolve. After that, take dilute 5 ml of the above solution and further make up with 100 ml with mobile phase. In Chromatographic condition, C18ODS-A column was used, other conditions was 250mm×4.6mm, 5µm and Flow rate 1.5ml/minute, Detection Wavelength 285nm, and Injection volume 20µl required and compared with standard and then assay was calculated. [9, 4, 6,10,11].

Accelerated Stability Study

Paracetamol and Mefenamic acid suspension was packed in 60 ml glass bottle. The packed bottles wereplaced in stability chamber maintained at 40 ± 2 ^{o}Cand 75±5% RH for 1 month. The samples were withdrawn after one month and were observed for changes on the physical parameter (i.e. change in colour, Assay,viscosity, any bad odour & pH).[12]

RESULTS

Appearance of suspension

Byvisually inspection, suspension shown in color was orange and viscous in nature.

Taste characterization

Eight Volunteers were selected to perform evaluation taste of suspension. When the batch (F1-F7) complexation formulations were evaluated by human volunteers, here F1 formulation use as a reference formulation for taste characterization, because of in this formulation not contain any ion exchange resin polymer. After 60 s evaluation of all batches formulation result was concluded that F7 formulation gives better complexation and it is completely mask the taste of bitter drug. Which confirmed that the bitter taste of Mefenamic acid was masked successfully. This is confirmed by the scale marking of the volunteers [7].

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Table 2: Taste Evaluation of Paracetamol and Mefenamic acid Suspension

Volunteers no./Batch no.	1	2	3	4	5	6	7	8
F1	3	3	3	3	3	3	3	3
F2	3	3	1	3	2	3	2	3
F3	2	2	2	2	3	2	2	3
F4	1	2	3	1	2	0	1	2
F5	3	3	3	2	3	3	3	3
F6	1	2	0	1	0	2	2	2
F7	0	0	1	0	0	0	0	0

Scale: 0 Good, 1 Tasteless, 2 slightly bitter, 3 Bitter, 4 Very bitter.

Confirmation of complexation in DRC

Formation of an ion exchange complex between Mefenamic acid and Doshion 544P was confirmed by FTIR studies.

The FTIR spectrum for Mefenamic acid show a weak peak at 3400 cm ¯1 due to the presence of a secondary amine. The broad band in the range of 3200-2900 cm due to the presence of –OH [1, 2]. The same also represents the intra-and intermolecular hydrogen bonding due to the –OH groups and also overlaps with the (–CH3) group. The peak at 1650-1750 cm¯1 is due to the presence of C=O group. The presence of a peak at 1000 cm ¯1 indicates the presence of a phenyl group. [22, 23]

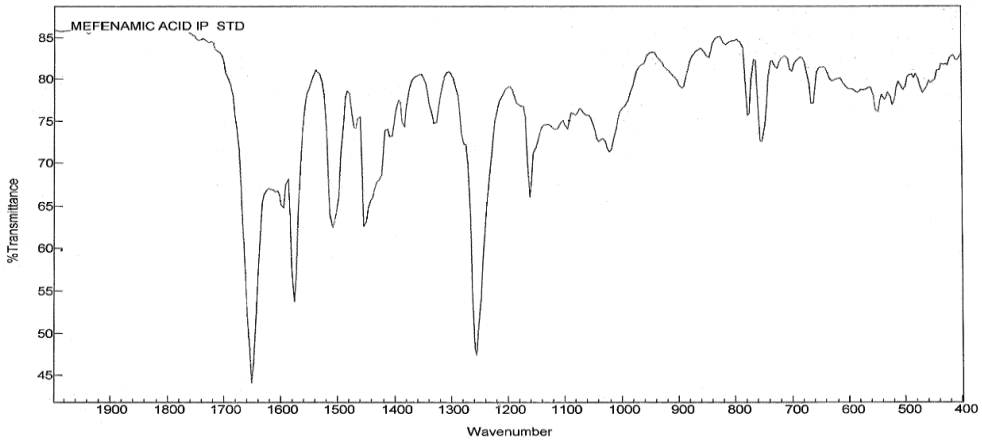

Figure 4: FTIR of Drug Mefenamic Acid

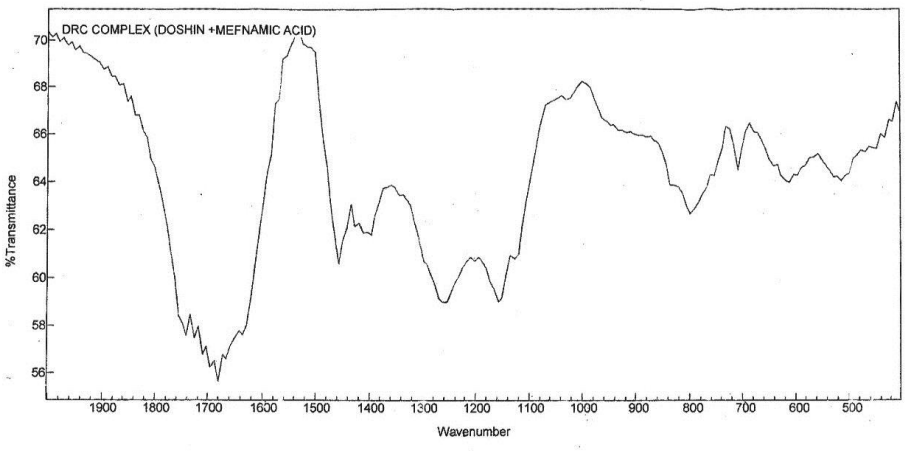

Figure 5: FTIR of DRC of Doshion 544P and Mefenamic Acid

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Determination of pH

pH of suspension was determined by the use of pH meter. And pH of all batch (F1-F7) gives satisfactory results. The result shown in (Table 3).

Viscosity of Suspension

The viscosity of all formulation weremeasure bybrook field viscometer DV-I prime spindle no.LV-3 (63) apparatus. So the all formulation were showsatisfactory results. but F7 gives best results.The sedimentation rate depends on the viscosity of the medium. The viscosity of the suspension is sufficient for the stability of the suspension. The result shown in (Table 3) [7].

Weight per ml

Weight per ml was of all batches formulation (F1-F7) measured by thoroughly clean and dry calibrated pycnometer. All formulations show suitable results, but F7 provides top result in this study. All observations were show in (Table 3).

Redispersability

Redispersability studies of all batches (F1-F7) conduct by placing 50 ml sample of all formulation respectively in the measuring cylinder, store for 10 days. Redispersability study was required, because of formulation take how much time required for use. All formulations were show different results but F7 show best result, after 10 days study. All batches results show in the (Table 3).[7]

Sedimentation

The sedimentation volume can have values ranging from less than 1. The ultimate height of the solid phase after settling depends on the concentration of solid and the particle size. To obtain an acceptable suspension the value of F should be at least 0.9. In the present formulation there is little sedimentation after 14 days and it could be easily redispersed to give a uniform dispersion after shaking for all the seven batches. The result of all formulation show less than 1 and all formulation comes under the range 0.9 that is the range of acceptance. The result shown in (Table 3).

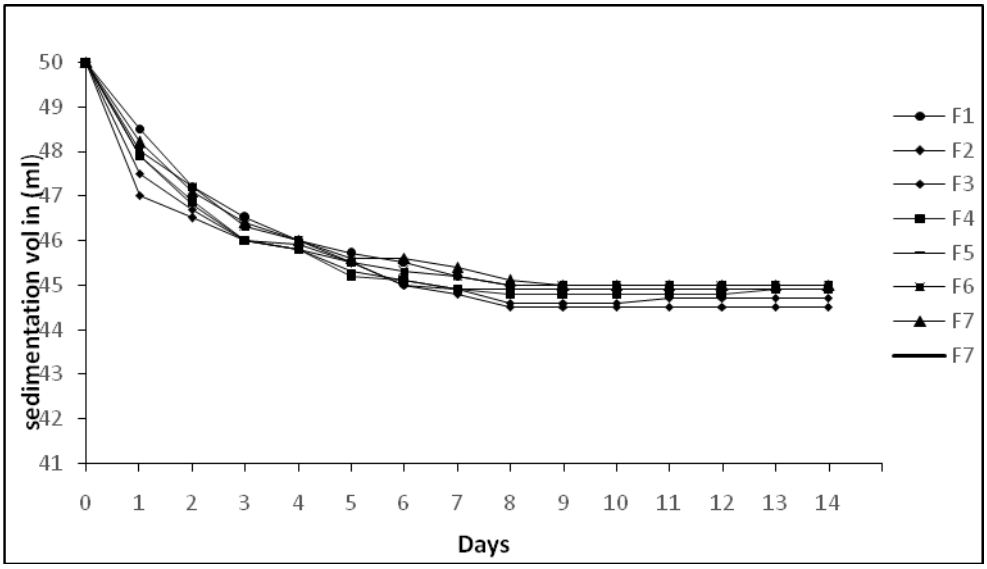

Figure 1: Sedimentation Volume of Paracetamol and Mefenamic acid Suspension

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Dissolution Profile of Paracetamol

Dissolution was carried out up to 30 m. All formulation F1 to F7 show the results were 99.90, 98.82, 98.80, 99.12, 98.92, 99.10, 99.95.Finally, F7 formulation was better observed than others formulation.

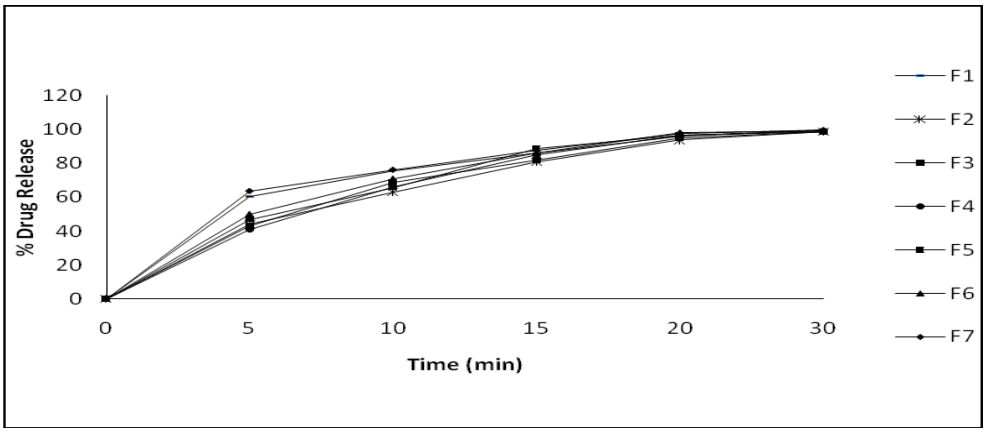

Figure 2: Drug Release Profile of Paracetamol

Dissolution Profile of Mefenamic acid

Dissolution was carried out up to 60 m. All formulation F1 to F7 show the results were 99.85, 98.65, 98.64, 98.89, 99.02, 99.10, 99.95. .Finally, F7 formulation was better observed than others formulation.

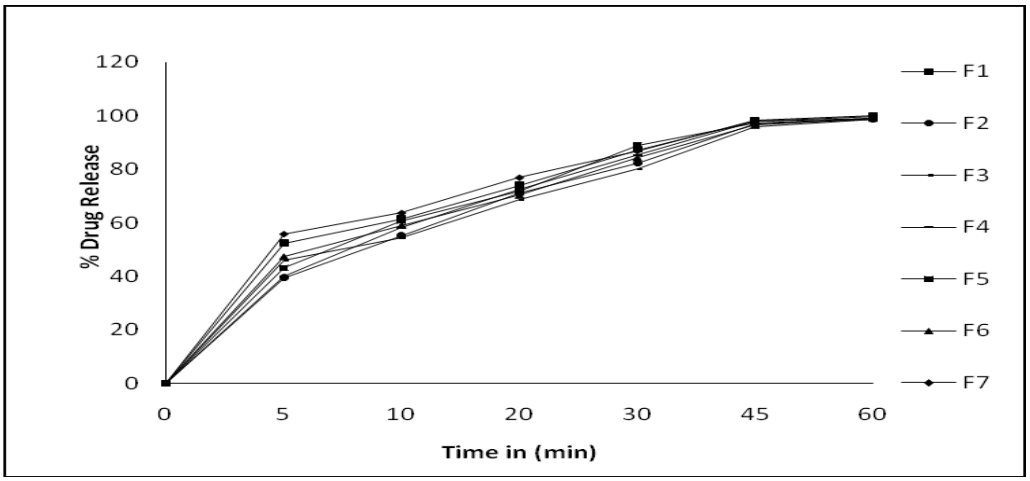

Figure 3: Drug Release Profile of Mefenamic Acid

Table 3: Evaluation Parameters of Paracetmaol and Mefenamic Acid Suspension with Different Resins

Parameters	F1	F2	F3	F4	F5	F6	F7
colour	Orange						
Taste	Bitter	Bitter	Slightly bitter	Slightly bitter	Bitter	Slightly bitter	Palatable
pH	6.64	6.43	6.34	6.38	6.49	6.42	6.65
Weight per ml (g/m)	1.2658	1.2649	1.2655	1.2650	1.2651	1.2659	1.2656
Viscosity(cps)	855	845	852	849	850	865	856
Redispersability(s)	80	72	75	70	77	79	81
Sedimentation	0.97	0.94	0.95	0.95	0.95	0.96	0.97
% Drug Release Paracetamol	99.90	98.82	98.50	99.12	98.92	99.10	99.98
% Drug Release Mefenamic acid	99.85	98.65	98.60	98.89	99.02	99.24	99.95
Assay (%) Paracetamol	99.921	98.710	98.642	99.011	98.800	99.254	99.989
Assay (%) Mefenamic acid	99.771	98.910	98.825	98.782	98.922	99.121	99.980

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DISCUSSION

In beginning, we choose a drug that have a bitter taste like Mefenamic acid and Paracetamol. For masking the bitter taste of Mefenamic acid and Paracetamol we select the Ion exchange resin polymers Kyron T-134 and Doshion 544P. After that we prepared Formulation F1 used as reference formulation because it was not contain any resin. Formulation of Paracetamol and Mefenamic Acid (F2, F3, F4) with Kyron T-134 was made in the ratio (1:1, 1:2, 1:3) respectively. Prototype formation of Paraceatmol and Mefenamic acid (F5, F6,F7) with Doshion-544P was made in ratio (1:1, 1:2, 1:3) respectively.(F2, F3, F4) formulation were rejected because of the bitterness of the formulation was not masked andalso the formulations show different Physical and chemical properties of the suspension. Formulation (F5, F6) were show bitter and slightly bitter in tastedue to the reason, bitter taste was not masked properly. So, Formulation (F5, F6) were also rejected.The formulation (F7) giveresults in all physical and chemical parameters. It gives orange colour, palatabletaste, pH 6.65, weight per ml 1.2656 (gm/ml), viscosity 856 (cps), redispersabaility 81 s, sedimentation rate 0.95, % drug release of Paracetamol 99.98, Mefenamic Acid 99.95, and assay of Paracetamol 99.989 & Mefenamic Acid 99.980. So, according to all formulation results, we conclude that the result of formulation (F7) was satisfactory in all parameters.

Accelerated Stability Study

Suspension of F7 was kept for accelerated stability study at 40 ± 2 ^{o}C and 75 ± 5% RH for 1 month in stability chamber. After a period of one month, the samples were observed for any change in physical parameters. It was observed that any change in colour. It was also noted that suspension was free of any kind of bad odour. Results obtained from the Evaluation after stability studies are shown in table 4. [11]

Table: 4 Evaluation Parameters after Stability Study of Paracetamol and Mefenamic acid Suspension F7

S.NO.	EVALUATON PARAMETERS	EVALUATION DATA BEFORE STABILITY STUDY	EVALUATION DATA AFETR STABILITY STUDY
1.	Color	Orange	Orange
2.	Taste	Palatable	Palatable
3.	pH	6.65	6.63
4.	Weight per ml (gm/ml)	1.2656	1.2649
5.	Viscosity (cps)	856	845
6.	Avg. net weight	60.25	60.24
7.	Redispersability (s)	81	80
8.	Sedimentation	0.95	0.94
9.	% Drug Release Paracetamol	99.98	99.97
10.	% Drug Release Mefenamic acid	99.95	99.94
11.	Assay of Paracetamol	99.989	99.980
12.	Assay of Mefenamic Acid	99.980	98.978

CONCLUSIONS

Children are frequently failed to take medications properly because of unpleasant taste of medicament. So that,a weak cation ion exchange resin complexation offers superior method for preparing taste-masked substrates of Mefenamic acid and paracetamol. It is a simple and effective technique for taste masking.Taste masked suspension of Mefenamic acid and paracetamol (F7) were successfully prepared using Doshion 544P as ion exchange resin by complexation method. Suspensions were evaluated for Particle size, viscosity, in vitro drug release, sedimentation volume, assay and taste evaluation. The taste of final trial was found totally masked & acceptable for the pediatric & geriatric patients. Mefenamic acid and paracetamol release from the developed formulations has been observed & it was found that resin was not retard the release of drug from suspension. Suspension of formulation F7 complies with quality control tests. Developed formulation F7 was found stable after the period of one month. It can be concluded that Doshion 544P has a maximum ability to mask the bitter taste of Mefenamic acid and paracetamol satisfactorily. Results obtained in this work shows that drug-resin complexes effectively masked bitter taste of Mefenamic acid. While liquid formulationprovide easier way to administer and getting the child to swallow.

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