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Kyron T-114 as an effective Precursor for development of fixed dose combination Orodispersible Formulation using taste masked Resinate

Deepesh Sahu[1], Om Prakash Sharma[2], Jatinder Dhari[2], Arun Kumar Sinha[2], Vijay Sharma[1]* and Kamla Pathak[1]

[1]Department of Pharmaceutics, Rajiv Academy for Pharmacy, N.H#2, P.O. Chhatikara, Mathura, Uttar Pradesh – 281001, INDIA

[2] Dr. Morepen Laboratory Ltd., Sector 2, Parwanoo, Distt.- Solan, Himachal Pradesh -17322, INDIA

Abstract

The objective of the present work was to develop taste masked fixed dose combination orodispersible tablet of dextromethorphan HBr (DXM), chlorpheniramine maleate (CPM) and phenylephrine HCl (PHE) using polymer (Eudragit E-100) and various grades of ion exchange resins (Kyron® and Tulsion®). The taste masking agents were explored for their effectiveness by investing drugs in ratios of 1:1, 1:2 and 1:3, with taste masking agents and coded as DS1 – DS18. After the evaluation for taste masking drug: Kyron T-114 (1: 3; DS6) was found as an effectively taste masked resinate and was optimized, evaluated for pharmacotechnical parameters, and characterized by diffuse reflectance spectroscopy, differential scanning calorimetry and surface morphology. DS6 was formulated as orodispersible tablets by direct compression and official and unofficial tests and orodispersion characteristics were evaluated. Resinate DS6 of DXM, CPM and PHE with Kyron T-114 in the ratio of 1:3 successfully masked the bitter taste of drugs in fixed dose combination and developed as orodispersible formulation (K1). Developed orodispersible formulation was subjected to evaluation for various evaluation parameters and was found unsatisfactory in terms of friability. Formulation K1 was then modified to K2 by adding PVP K-30 that exhibited desired friability and displayed a dissolution efficiency of 94.70±2.46% for DXM, 89.45±0.92% for CPM and 96.83±1.39% for PHE at 45 min. The study highlighted the importance of development of an orodispersible dosage form for administration of taste masked resinates to geriatric and pediatric patients, for effective management of cough, cold and allergy.

*Corresponding author, Mailing address:
Vijay Sharma, Associate Professor
Department of Pharmaceutics, Rajiv Academy for Pharmacy, Mathura, Uttar Pradesh – 281001, INDIA.
E.mail: vijay_ceutics07@yahoo.co.in

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INTRODUCTION

Patients suffering from cold may suffer from other symptoms like cough, congestion, itching, running nose, watery eyes and allergy. The use of any single drug in a dosage form is not justified to cover all the

three symptoms effectively hence there is a need of dosage form that contains combination of drugs used for the treatment of symptoms that improve patient compliance. Dextromethorphan hydrobromide is a non-narcotic widely used antitussive agent generally used as an active ingredient in cough and cold remedies having a central effect on the cough center in the medulla oblongata and is used for the treatment of respiratory disorders. [1,2] Chlorpheniramine maleate, a weakly basic water-soluble cationic drug with H_1-histaminic receptor antagonist used extensively for symptomatic relief of the common cold and allergy.[3,4] Phenylephrine hydrochloride is a sympathomimetic drug used during nasal congestion, sinusitis and rhinitis.[5] As the drugs have amine as one of the functional groups, which is responsible for their obnoxious/ bitter taste.[6]

Taste-masking is a critical issue in the development of orodispersible tablet containing bitter drugs.[7] Various taste masking approaches have been exploited to solve the problem associated with unpleasant taste of drugs. Conventional taste masking techniques such as the use of sweeteners and flavoring agents alone are often inadequate in masking the taste of highly bitter drugs.[8] Ion exchange resin (IER) provides alternative method for taste masking, are water-insoluble, high molecular weight polyelectrolyte's cross linked polymer containing salt forming groups in repeating positions on the polymer chain that can exchange their mobile ions with equivalent charge present in the surrounding medium reversibly and stoichiometrically, and available in different grades.[4] the ion exchange resins are predominantly vinyl, divinyl benzene and polystyrene copolymers. As high molecular weight polyelectrolyte's having extensively charged functional sites, [9] bitter cationic drugs get adsorbed on to the weak cation ion exchange resin having carboxylic acid functional groups and mask the bitter taste. The selection of ion exchange resins should be made on the basis of nature of drug and can be selected from the class of cation exchange resin and anion exchange resin. Resinate of drug with resin can be easily formulated as lozenges, chewing gum, suspension or dispersible tablet.[10]

The present study is aimed to develop a pharmaceutically equivalent taste masked orodispersible formulation of undisclosed technology in order to generate useful data to generalize the technique and to provide opportunities to the researchers for further improvement in the formulation perspectives related to fixed dose combination containing bitter drugs, for effective management of cough cold and allergy.

MATERIALS AND METHODS

MATERIALS

Dextromethorphan HBr was obtained from (Dr. Reddy's Lab Ltd., Banjara Hills, Hyderabad), Chlorpheniramine maleate from (Supriya Chemicals Pvt. Ltd., Goregaon (East) Mumbai, India), Phenylephrine HCl from (Malladi Drugs and Pharmaceuticals, Chennai, Tamilnadu). Eudragit E-100 was procured from (Degussa India Pvt. Ltd., Mumbai, India), Kyron T-114, Kyron T-154 and Kyron T-134 and was purchased from (Corel Pharma Chem., Ahmedabad, Gujarat, India).Tulsion T-42 and Tulsion T-52 were obtained from (Thermax India Ltd., Pune), Sodium starch glycolate I.P. and Poly vinyl pyrrolidone K-30 I.P. were procured from (Morepen Labs Ltd., Baddi, Solan, Himachal Pradesh, India), Color sunset yellow lakes was obtained from (Narmada Colors Pvt. Ltd., Bhavnagar, Gujarat), Flavor orange was obtained from (Cargill India Pvt. Ltd., Prakash Nagar, Bangalore). All other solvents and requirements are of HPLC grade or analytical grade.

METHODS

TASTE MASKING OF BITTER DRUGS

To mask the bitter taste of DXM, CPM and PHE in combination, two approaches namely polymer

dispersion using Eudragit E-100 and resinates using different grades of ion exchange resins, were employed.

Preparation of polymeric dispersion

Accurately weighed amount (8.5 g, 17.0 g and 25.5 g) of Eudragit E-100 was dissolved separately in ethanol (10% v/v) with continuous stirring (300 rpm) in a 500 ml of glass beaker to prepare polymeric solutions. Five grams of DXM, 1 g of CPM and 2.5 g of PHE were accurately weighed and mixed with prepared polymeric solution to satisfy drug: Eudragit E-100 ratios of 1:1, 1:2 and 1:3 (Table 1) until uniform dispersions were obtained. The dispersions were separately spread in trays, dried at 25°C and the dried mass was scrapped with spatula. The scrapped products were coded as (DS1 – DS3) and stored in a dessicator till further use.

Preparation of resinates by Batch method

Accurately weighed amount (8.5 g, 17.0 g and 25.5 g) of the ion-exchange resins were added separately to 100 ml deionized water with continuous stirring (300 rpm) in 500 ml glass beakers to prepare homogenous dispersions. Accurately weighed 5 g of DXM, 1 g of CPM and 2.5 g of PHE were mixed with resin dispersion (Table 1) with continuous stirring (300 rpm) for 3–4 h. The pH of the system was maintained at 6.0- 6.5 using 1.0 M KOH solution. Resinates were washed with three portions of 75 ml of deionized water, dried at room temperature, and coded as DS4 – DS18, (Table 1) and stored in desiccators till further use.

EVALUATION OF TASTE MASKED DISPERSIONS/RESINATES

***In-vivo* evaluation for taste masking**

Eighteen healthy human volunteers in the age group of 18-24 years were selected to assess the degree of taste masking of polymer dispersion and resinates after obtaining their written consent. The polymeric dispersions (DS1 – DS3) and resinates (DS4 - DS18) were evaluated for taste masking by placing the test sample on the posterior lobe of tongue for 4-6 sec, spitting out and rinsing the mouth with water. The perception of taste was noted and reported (000: Extremely bitter, 00: Very bitter, 0: Moderately bitter, +: Slightly bitter, ++: No perception of bitter taste). The study was conducted in manner such that same set of volunteers were used for taste evaluation of polymeric dispersions and resinates on consecutive days. The taste masked product was identified.

Diffuse reflectance spectroscopy

DRS studies were carried out, using FTIR Spectrophotometer (Shimadzu FTIR-8400S Kyoto, Japan) with DRS attachment. The KBr powder (IR grade) was grounded in a glass mortar and placed in the sample cup of the DRS attachment, surface of powder was pressed using sample pressing bar. The powder was then mounted to the instrument to record background measurement. The test sample(s) was diluted with KBr powder and grounded to get a fine mix. The DRS was recorded between the ranges of 400-4000 cm^{-1} in the transmittance % T mode.

Differential scanning calorimetry (DSC)

The thermal behavior of the pure DXM, CPM, PHE, KyronT-114 and DS6 was recorded on differential scanning calorimeter (DSC Q-200 V 24.4 Build 116, TA instruments, USA). Samples were accurately weighed and placed in aluminum pan and sealed with lid. Aluminum oxide was used as the reference. Heating rate of 10 °C/min was applied at the range of 50 to 300°C with nitrogen purge of 0.2 ml/min.

Surface morphology

The surface morphology of pure DXM, CPM, PHE, KyronT-114 and resinate was studied by scanning electron microscope (Q 200 TA 200 Instrument V 24.4 Build 116, USA). The samples were coated with gold palladium under an Argon atmosphere using a gold sputter module in a high vacuum evaporator.

The coated samples were then observed with a scanning electron microscope at the magnification of 200 X.

Pharmacotechnical Characterization

Rheological characterization`

Angle of repose (θ) was determined using fixed height cone method. The blend was poured through a funnel that can be raised vertically until a maximum cone height obtained.[11] Radius of the heap was measured and angle of repose was calculated by using following equation. [12]

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

Where θ = Angle of repose, h = height of pile and r = radius of pile

Bulk density of resinates was also determined, as per the method described by Martin.[13] The bulk density was calculated using following equations:

$$\text{Poured Density} = \text{Wt. of resinate/Bulk vol. of resinate} \quad (2)$$

$$\text{Tapped Density} = \text{Wt. of resinate/Tapped vol. of resinate} \quad (3)$$

% Compressibility index (CI) and Hausner's ratio were calculated by using following equations:

$$\%CI = \text{Tapped Density} - \text{Poured Density/Tapped Density} \times 100 \quad (4)$$

$$\text{Hausner's Ratio} = \text{Tapped Density/Poured Density} \quad (5)$$

Particle size analysis and skewness

The average particle size of prepared resinate was determined by optical microscopy, and mean particle size was calculated by measuring size of 500 particles using calibrated ocular micrometer (Hicon ®, Grover Enterprises, Delhi). The data obtained was plotted on a probability scale to determine average particle size (d_{mean}) and standard deviation. The % cumulative frequency undersize curve was used to determine the interquartile coefficient of skewness (IQCS). [13]

IQCS of resinates was determined by using following equation.

$$IQCS = (c-a) - (a-b)/ (c-a) + (a-b) \quad (6)$$

Where a is mean diameter, b and c are the lower and upper quartile points in the cumulative frequency distribution curve.[14]

PREPARATION OF TASTE MASKED ORODISPERSIBLE TABLETS

Taste masked orodispersible tablets were prepared by mixing accurately weighed amount of DS6 with, superdisintegrant, sweetening agent, flavoring agent, coloring agent and other directly compressible excipients listed in Table 2. The blend was directly compressed to tablets in a rotary compression machine (16- Station, Cadmach, Ahmedabad, India).

EVALUATION OF ORODISPERSIBLE TABLETS

Friability and Hardness

Friability of orodispersible tablets was determined by using Roche friabilator (HICON®, Grover Enterprises, New Delhi, India), 10 tablets from each batch were selected at random and weighed accurately. Tablets were then placed in a plastic chamber that rotates at 25 rpm dropping tablets from a distance of six inches with each revolution. The friabilator was then operated for 100 revolutions after that tablets were dusted and reweighed. Friability was calculated by using following equation.[15]

$$\%\ \text{Friability} = \text{Initial wt.} - \text{Final wt./ Initial wt.} \times 100 \quad (7)$$

Six tablets from each batch were taken at random and hardness of the prepared orodispersible tablets was measured by using Monsanto hardness tester. The mean of six determinations was obtained and the result is reported in kg/cm.

Wetting time and water absorption ratio

Five circular tissue papers of 10 cm diameter were placed in a petridish of 5 cm internal diameter. 5 ml of water containing methylene blue (0.1% w/v) was added to the petridish. A preweighed tablet was carefully placed on the surface of tissue paper and the time required for the dye to reach the upper surface of the tablet was recorded and reported as wetting time. The tablet was then carefully reweighed and the weight obtained was obtained was used to calculate water absorption ratio (R) by using following equation.[16]

$$R = Wa - Wb / Wa \times 100 \quad (8)$$

Where, Wb = Weight of tablet before water absorption and W_a = Weight of tablet after water absorption.

Weight variation

Twenty tablets of each batch were selected randomly and weighed. The average weight was calculated, not more than two of individual weight deviated from the average weight by more than the percentage as per limits and not deviated more than twice that percentage.[15]

***In-vitro* disintegration time**

The disintegration time of the prepared orodispersible tablets was determined by using U.S.P. disintegration test apparatus (ED-06, Electro lab, Mumbai, India) containing 900 ml phosphate buffer pH 6.8 as a disintegrating media maintained at 37°C ± 2°C. Time was recorded when all the fragments of orodispersible tablet passed through the screen of the basket. [17] A mean of three determinations was recorded and reported in seconds, as *in-vitro* disintegration time.

***In-vitro* drug release**

Drug release from orodispersible tablet containing was determined using USP Dissolution apparatus (Electro lab TDL-08L) type II (paddle type) in 500 ml of simulated gastric fluid (SGF, pH 1.2) containing 1%w/v sodium lauryl sulfate maintained at 37±2°C. Dissolution test was performed at 75 rpm for 45 min. An aliquot was withdrawn from the dissolution medium at 45 min and the amount of DXM, CPM and PHE released was estimated accurately using HPLC.

HPLC Methodology

A gradient high-pressure liquid chromatography (Waters 2695, Milford, US) with UV/VIS Detector and RP C-18 column (250×4.6 mm I.D, particle size 5µm) was used. DXM, CPM and PHE samples (0.5ml) were filtered through a 0.2 µm membrane filter and injected into the column at a flow rate of 1.2 ml/ min, the mobile phase (acetonitrile) that was filtered through a 0.45 µm nylon disc filter before use. The eluants were detected by HPLC (Waters 2695, Milford, US) with UV/VIS detector at 220 nm. The peak areas of DXM, CPM and PHE were determined.

RESULTS AND DISCUSSION

Taste is considered as an important parameter for orodispersible tablets since the tablet disintegrates in oral cavity and the taste of its constituents is perceived in mouth. DXM, CPM and PHE are bitter drugs and taste-masking is prime prerequisite to enable their delivery through orodispersible technologies. A variety of taste masking technologies have been reported in literature and the selection is based on the physicochemical characteristics of the drug in question. Use of ion exchange resins is particularly suitable for taste masking of water soluble drugs. Therefore ion exchange resins Kyron T-114, Kyron T-154, Kyron T-134, Tulsion T-42, and Tulsion T-52 were explored for taste masking of DXM, CPM and PHE in addition to polymeric dispersion made with Eudragit E100.

Healthy human volunteers confirmed the bitter taste of DXM, CPM and PHE and the bitter taste was also perceived with polymeric dispersions DS1- DS3. With the exception of DS6, rest all the failed to mask the

bitter taste of drugs (Table 3).The taste was effectively masked in DS6 prepared with Kyron T-114 in a ratio of 1:3. The resinates of Kyron T-114 also offer the advantage of stability, both in salivary pH 6.7 and at cation concentration of about 40meq/L in the saliva, and are reported to offer resistance to breakdown in the oral cavity.[18]

The reasons for the failure of certain ion exchange resins used for taste masking are co-relatable with several parameters that affects are- the functional group present in ion exchange resins other than Kyron T-114, is the sulphonic acid functionality which restricted their use as taste masking agents and they are the derivative of polystyrene matrices that have low ion exchange ability (4meq/gm) due to presence of bulkier ionic substituents.[19] Apart from this poor swelling properties and high degree of brittleness results in ineffective adsorption of drugs on to the surface of resin and hence incomplete taste masking.

Kyron T-114 is an acrylic acid derivative and its efficiency as taste masking agent is associated to the presence of carboxylate functional groups and its high purity, finding its use in pharmaceutical formulations for drugs containing amino group.[20] Additionally, Kyron T-114 exhibits low particle size that imparts large surface area and promotes high drug loading.[21] All these features resulted in efficient taste masking of bitter tasting drugs concomitantly. Thus DS6 was selected for characterization and formulation development.

Diffuse reflectance spectroscopy

The DRS spectra of DXM, CPM and PHE showed prominent peaks at 2589.36, 2470.69 and 2807.61 cm^{-1} (Figure 1) indicating the presence of NH^{+1} (DXM and CPM) and NH_2^+ (PHE) due to stretching vibration of the tertiary and secondary amine salt. The DRS spectra of Kyron T-114 showed three broad stretching vibrations at 3550.36, 1751.44 and 1284.01 cm^{-1} that were assigned to O-H, C=O and C-O respectively.[22] In case of DS6 the distinctness of the stretching bands of DXM,CPM and PHE was lost and emergence of broad multi-peaked band was recorded. These peaks, characteristic of the drugs shifted towards left at 2761.21, 3050.36 and 3258.32 cm^{-1} for DXM, CPM and PHE respectively. The emergence of broad multi-peaked band was marked with disappearance of peak at 3550.36 cm^{-1} of Kyron T-114 that clearly signifies chemical interaction between the ion exchange resin and the drugs.[23-24] However the peaks at 1751.24 and 1284.51 for C=O and C-O respectively were distinctly retained in DS6. Thus the ion exchange can be assumed to have taken place at -OH of KyronT-114.[25-26]

Differential scanning calorimetry

The thermograms of DXM, CPM and PHE exhibited sharp endothermic peak at 123°C, 135°C and 145°C respectively (Figure 2) with no apparent decomposition up to a temperature of 300°C. Kyron T-114 exhibited broad endothermic asymmetrical peak between 50–150°C with melting point at 61°C that was retained in DS6 indicating that the drugs were not in their native forms in resinate.[27] However the peak of DS6 spectra was less asymmetrical than melting peak of Kyron T114 and the melting point shifted to 78 °C confirming the chemical interaction between drugs and resin. The shift in melting point lowering and broadness of endothermic peak in case of the resinate (DS6) in the presence of DXM, CPM, PHE and Kyron T-114 is attributed to the dilution effect of the ion exchange resin that resulted in a reduction of the intensity of endothermic peak exhibited by resinate containing all the three drugs.[2] These results are consistent with DRS results and with the reports made by Malladi and his coworkers.[24]

Surface morphology

The micrographs of DXM exhibited irregular shaped prismatic crystals of various size (Figure 3A), CPM was observed large cubic irregular shape particles (Figure 3B), and while of PHE was blend of large and fine particles of pointed edges (Figure 3C). The

micrographs of Kyron T-114 displayed a blend of large irregular and perfect spherical particles with smooth surface (Figure 3D and E). The resinate of DS6 showed deposits of drug(s) particles on the surface of Kyron T-114 (Figure 3F), that was the result of physical bonding due to deposition of drugs on the surface of Kyron T-114, this evidences a possibility of strong ionic bonding between drugs and ion exchange resin, due to which the drugs will not be release freely at salivary pH.

Pharmacotechnical characterization

DS6 exhibited good flow property as angle of repose was 25±0.25°. Its bulk density was 0.55±0.31gm/cm^3 and the tapped density increased very to 0.65±0.67gm/cm^3. The difference in tapped and bulk density was low suggesting wide particle sized distribution. The % compressibility index of 13±0.15 affirmed good flow properties. Hausner's ratio of 1.17±1.18, also proved good flowability of DS6 that is useful feature for large scale manufacturing.

The average mean particle diameter was 20 µm and the particles size distribution when summarized using statistical methods exhibited IQCS value of 0.698 indicating high degree of skewness. If the IQCS value is zero the size distribution is practically symmetrical. The IQCS value thus obtained indicated an asymmetrical distribution and value of standard deviation indicates that the resinate particles are uniformly sized.[14]

PREPARATION AND EVALUATION OF ORODISPERSIBLE TABLETS

Taste masked orodispersible tablets of DS6 were successfully prepared by direct compression method and subjected for the evaluation of various formulations related parameters. The formulation K1 exhibited a friability of more than 1%. Hence, new formulation K2 was proposed using of PVP K-30 as binding agent. On evaluation K2 showed a friability value was less than 1% that meets the pharmacopoeial limit[15] and the hardness of K2 formulation was 3.0±0.5 kg/cm indicating that the formulation is mechanically stable. The improved friability of K2 formulation is attributable to the binding property of PVP K-30 and other favored characteristic is its rapid dissolution in water that contributes to high drug release. Both K1 and K2 formulations pass weight variation test as the percent weight variation was within the pharmacopoeial limits.[15]

Wetting time and water absorption ratio

The wetting time of both K1 and K2 formulations was close at 18 ± 2.5 and 17 ± 0.4 sec. respectively while the water absorption ratio differed markedly (60±0.5 and 82.1±1.5 % for K1 and K2 respectively. The presence of PVP K-30 along with sodium starch glycolate (superdisintegrant) used in the tablet formulation facilitate water uptake due to high swelling property that allows water to enter the tablet matrix and is responsible for the faster and larger volume of water uptake exhibited by formulation K2.[28] The similar mechanism has been reported by Fayed and his coworker, that if a matrix containing swellable polymer comes in contact with aqueous medium, an abrupt change takes place in its physical state i.e. conversion from rigid physical form of polymer to rubbery state,[2] which is associated with the swelling process that facilitates the process of ingresment of water resulted in high water absorption ratio.[29]

***In-vitro* disintegration time**

The *in-vitro* disintegration time of K1 and K2 complied with the pharmacopoeial limit of less than 3 min[30] for orodispersible tablet. The disintegration time was found to be 54±0.44 and 32±0.76 sec for K1 and K2 respectively. The less disintegration time of K2 was due to the presence of PVP K-30 that exhibit excellent water ingressing property due to its highly hydrophilic nature facilitates faster disintegration of tablets leading to accelerated dissolution.[31] On the basis of low friability, wetting time, water absorption

ratio and *in-vitro* disintegration time formulation K2 was selected and subjected to drug content determination and i*n-vitro* drug release study.

Drug content determination and *In vitro* drug release

The percent drug content of K2 formulation was estimated to be 99.17±2.41%, 98.85±0.32% and 98.42±0.13% for DXM, CPM and PHE respectively. The drug release study was conducted in simulated gastric fluid (SGF) and not in simulated salivary fluid based on the following considerations. Upon oral administration, an orodispersible tablet is expected to rapidly get converted to uniform dispersion in the oral cavity,[32] but due to the low concentration of H^+ in salivary fluid the resinate is expected not to release the drugs in oral cavity. Thus salivary fluid was not selected for the *in-vitro* drug release study. The resinate is however, weak enough to be broken down by the abundance of H^+ ion in SGF that would lead to the release of drugs and hence selected for the drug release determination. The release profile was assessed by dissolution independent parameters. Formulation K2 displayed a dissolution efficiency of 94.70±2.46% for DXM, 89.45±0.92% for CPM and 96.83±1.39% for PHE at 45 min. The results depict the efficiency of K2 in releasing the drugs in SGF. Drug release in SGF occurred due to exchange of ion between resinate and release media. The presence of H^+ in the SGF caused displacement of DXM, CPM and PHE facilitating drug release. The drug-release equilibrium, similar to drug loading, is highly dependent on the physiological pH can be applied for taste masking without affecting the dosage form characteristics.[33] Other contributing factors are- weak cation resin that cannot sustain the drug release and small particle size of resinate resulting in large surface area that lead to quick exchange of bound drug from the resinate particles.[34]

Conclusion

The use of ion exchange resin Kyron T-114 successfully masked the bitterness of DXM, CPM and PHE concomitantly and generated the possibility of developing an orodispersible tablet an adapted dosage form for geriatric and pediatric patients.

Declaration of interest

The authors report no conflicts of interest.

Table 1: Different ratios of drug: eudragit E-100/ ion exchange resin for preparation of taste masked dispersions/resonates

Drug/Taste Masking Agents	Amount of Drug and Taste masking agent (mg)																	
	DS 1	DS 2	DS 3	DS 4	DS 5	DS 6	DS 7	DS 8	DS 9	DS 10	DS 11	DS 12	DS 13	DS 14	DS 15	DS 16	DS 17	DS 18
DXM	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
CPM	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
PHE	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Eudragit E-100	17	34	51	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Kyron T-114	-	-	-	17	34	51	-	-	-	-	-	-	-	-	-	-	-	-
Kyron T-154	-	-	-	-	-	-	17	34	51	-	-	-	-	-	-	-	-	-
Kyron T-134	-	-	-	-	-	-	-	-	-	17	34	51	-	-	-	-	-	-
Tulsion T-42	-	-	-	-	-	-	-	-	-	-	-	-	17	34	51	-	-	-
Tulsion T-52	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	17	34	51

Table 2: Composition of orodispersible tablets of DXM, CPM and PHE in combination

Ingredients (mg/tablet)	Formulation Code	
	K1	K2
Drugs: Kyron T-114 (Resinate DS6)	68.00	68.00
Microcrystalline Cellulose	120.00	120.00
Polyvinyl pyrrolidone K-30	0.00	6.00
Sodium starch glycolate	12.00	12.00
Sorbitol	150.00	150.00
Mannitol	60.00	60.00
Citric acid	6.00	6.00
Orange flavor	9.00	9.00
Aspartame	3.00	3.00
Sunset yellow lake color	0.5.0	0.5.0
Talc	6.00	6.00
Magnesium stearate	6.00	6.00
Lactose anhydrous (DCL-15)	q.s	q.s
TOTAL WEIGHT(mg)	**600**	**600**

Table 3: Comparative *in-vivo* taste evaluation of prepared polymeric dispersions/resonates

Drug(s)/Eudragit E-100/ Resins	Complex Code	Drug: Eudragit E-100/ Resin Ratio	Bitterness Level
DRUG(S) Eudragit E-100	--	--	000
	DS 1	1:1	00
	DS 2	1:2	0
	DS 3	1:3	0
Kyron T-114	DS 4	1:1	00
	DS 5	1:2	+
	DS 6	1:3	++
Kyron T-154	DS 7	1:1	00
	DS 8	1:2	0
	DS 9	1:3	0
Kyron T-134	DS 10	1:1	00
	DS 11	1:2	0
	DS 12	1:3	0
Tulsion T-42	DS 13	1:1	00
	DS 14	1:2	0
	DS 15	1:3	0
Tulsion T-52	DS 16	1:1	00
	DS 17	1:2	0
	DS 18	1:3	0

000: Extremely bitter; 00: Very bitter; 0: Moderately bitter; +: Slightly bitter; ++: No perception of bitter taste

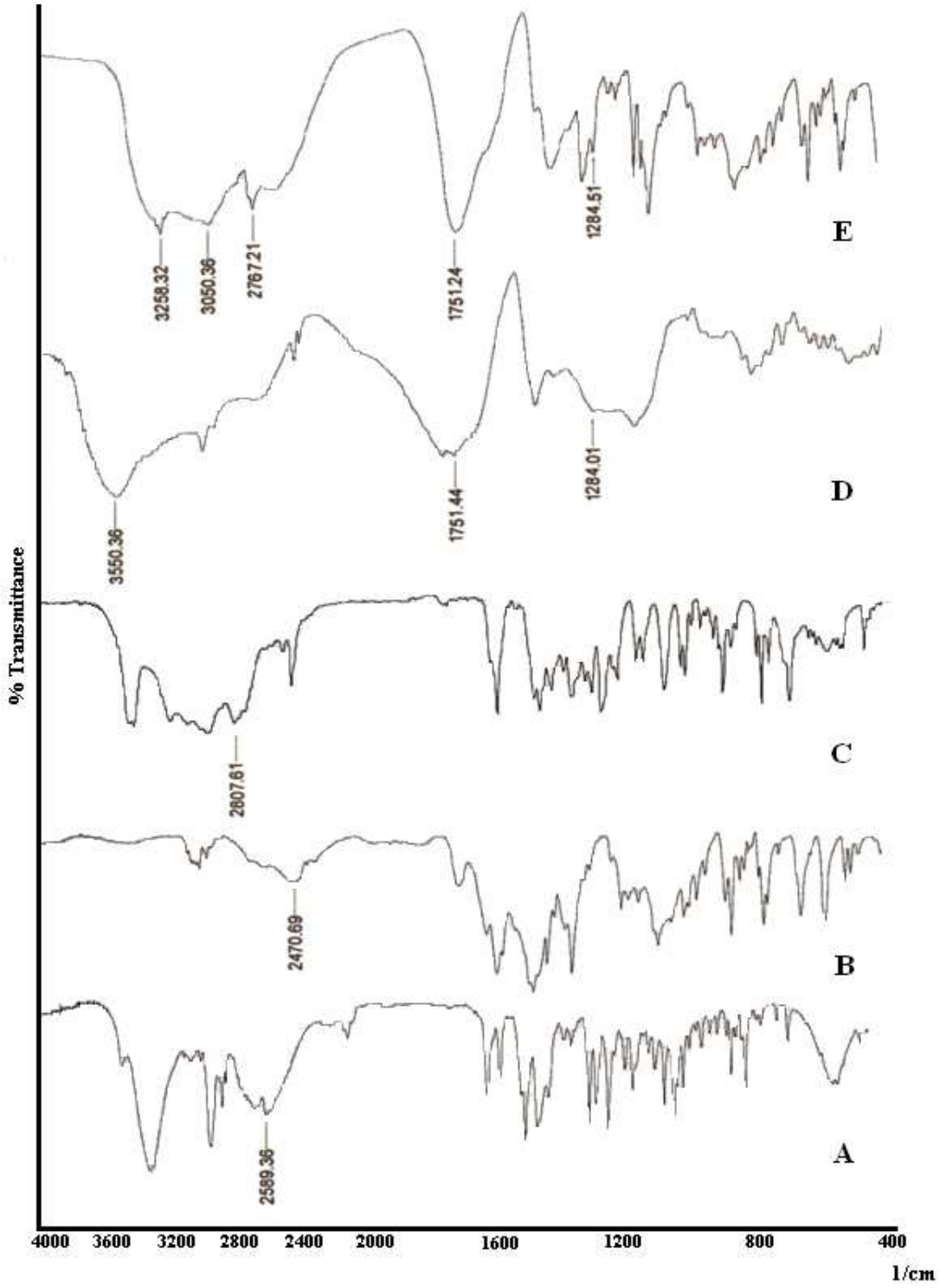

Figure 1: DRS Spectra of A) DXM, B) CPM, C) PHE, D) Kyron T-114 and E) Resinate (DS6)

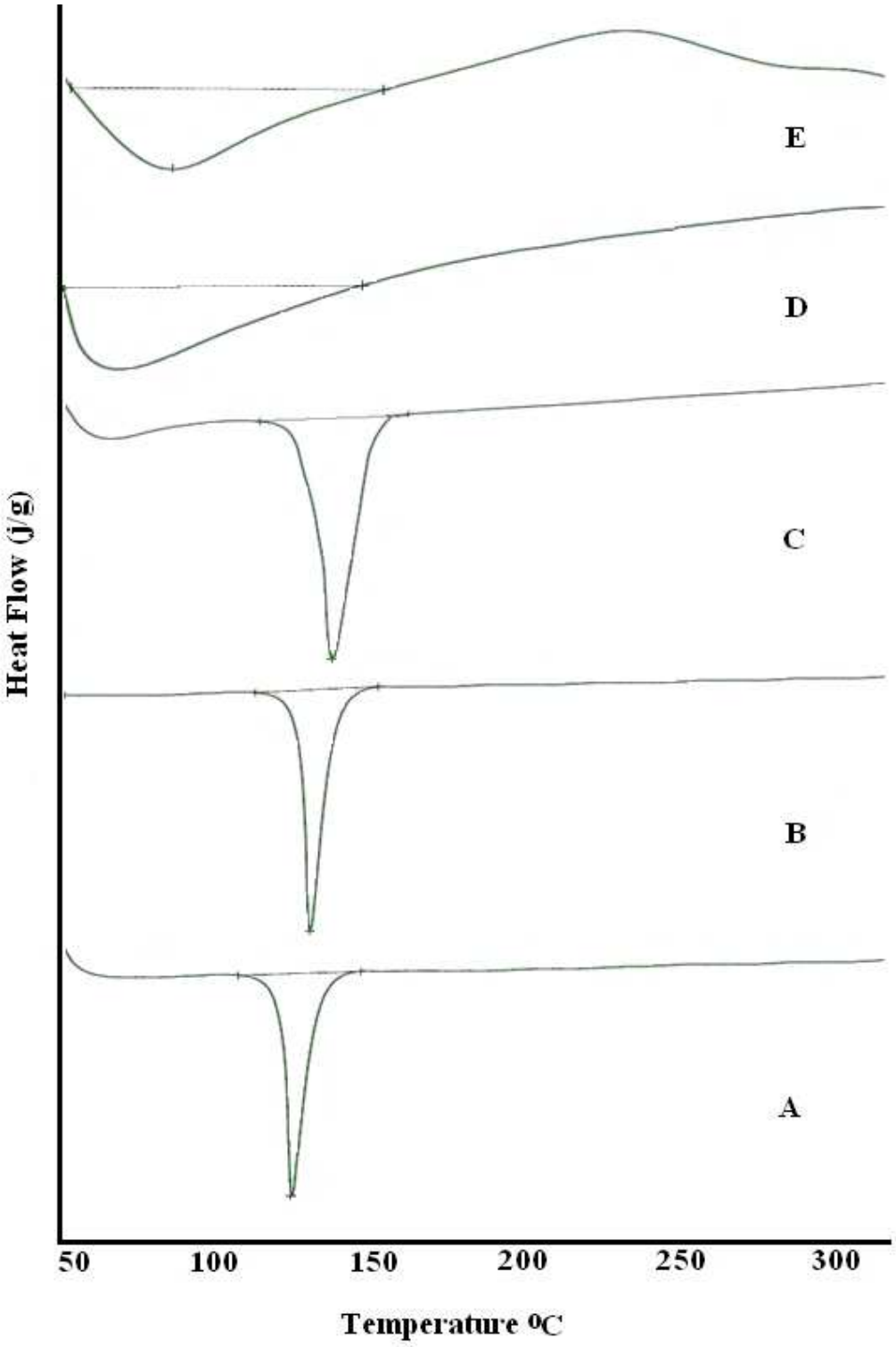

Figure 2: DSC Thermogram of A) DXM, B) CPM, C) PHE, D) Kyron T-114, E) Resinate (DS6)

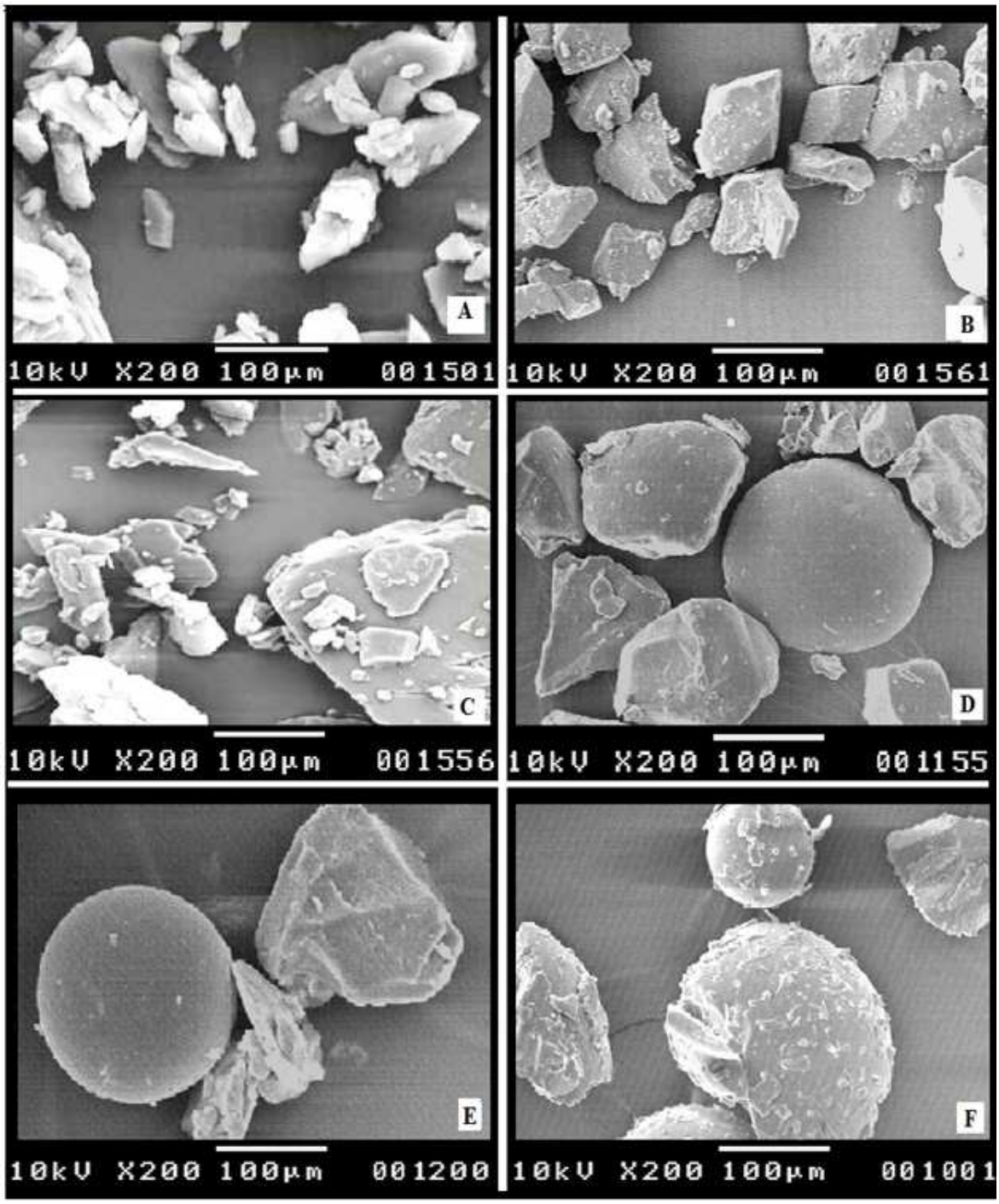

Figure 3: SEM photomicrographs of A) DXM, B) CPM, C) PHE, D&E) Kyron T-114, F) Resinate (DS6)

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