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ROSIN MICROSPHERES AS TASTE MASKING AGENT IN ORAL DRUG DELIVERY SYSTEM

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ABSTRACT

Natural resources in general and plant materials in particular are receiving more attention due to their safety as pharmaceutical excipients. Present work assessed the combination potential of natural hydrophobic resin, rosin, and synthetic polymer ethyl cellulose to mask the abhorrent inherent taste of ambroxol hydrochloride, by microencapsulation technique, and its possibility to formulate as a fast dissolving dosage form. Being of natural origin, rosin and its derivatives are biodegradable and biocompatible. Although It has excellent film forming property the native rosin films are brittle and break easily upon handling. The film forming properties of rosin was modified by substituting a part with ethyl cellulose.The prepared rosin-ethyl cellulose composite microspheres by emulsion solvent evaporation technique possessed good sphericity, smooth surface morphology, uniform and narrow size distribution (10–90 µm), when analyzed by scanning electron microscopy. PEG 400 was used as plasticizer because of its hydrophilicity, biocompatibility and their excellent plasticizing activity. Method of preparation has influenced the particle size and drug loading efficiency. Drug-polymer compatibility was confirmed by Fourier transform infrared spectroscopy and thin layer chromatography. DSC studies revealed that the drug was molecularly dispersed inside the microspheres in the form of solid solution. Sensory studies in healthy human volunteers indicated that the taste and palatability were significantly improved by microencapsulation. This study demonstrated that rosin could be a right choice in developing patient favored formulations for bitter drugs and can be utilized in fast disintegrating dosage forms as well.

INTRODUCTION: Plant materials contributed significantly to the repertoire of medicines since ancient times, are screened for their use as pharmaceutical adjuvant too. Many synthetic, semi synthetic and naturally occurring polymers have been found favor as release retarding components in microsphere preparation. Some of these naturally occurring materials include lipids, waxes, albumin, gelatin, polysaccharide like alginate and chitosan [1–3].

In the present study, we report the novel application of a natural hydrophobic resin, rosin as taste masking agent in the oral drug delivery system. Rosin, is a solid resin obtained from Pinus palustris Miller and other species of Pinus linnae.It is composed of approximately 90% of rosin acids, prominent ones include abietic acid and have a typical molecular formula $C_{20}H_{30}O_2$. The oral toxicity (LD_{50}) studies on guinea pigs have proved rosin being practically nontoxic [4].

It has been investigated for microencapsulation, film forming and coating properties, matrix materials in tablets for sustained and controlled release [5–7]. In recent years the importance of patient compliance and overall economics of healthcare is been increasingly recognized. Orally disintegrating tablets offers various advantages to the end users. However, taste masking is highly desirable but challenging while developing oral disintegrating formulations of bitter drugs. One of the feasible techniques to accomplish the taste masking is by preparing the microparticles. Review on the literature revealed that majority of the polymers used for taste masking are synthetic, enteric in nature and require organic solvent based microencapsulation technique.

The glass transition temperature (T_g) of rosin is less than 30^{o}C and thus it is difficult to process and use at room temperature. Although it has excellent film forming property native rosin films are brittle and break easily upon handling [8]. However, rosin can be modified into a useful film former for various pharmaceutical applications [9]. The main use of ethyl cellulose in oral formulations is as hydrophobic coating agent for tablets and granules [10-12]. Ethyl cellulose coatings are used to modify the release of a drug, to mask an unpleasant taste, or to improve the stability of a formulations.

In the current study, we have modified the film forming properties of rosin by substituting a part with ethyl cellulose. We have also selected PEG 400 as plasticizer because of its hydrophilicity, bio-compatibility and their excellent plasticizing activity. In addition modification may also improve its safety and stability in oral formulations.

The purpose of the current study was to characterize rosin-ethyl cellulose films and to prepare rosin-ethyl cellulose composite microspheres by emulsion solvent evaporation technique.

Another objective of the study was to assess the viability of these microspheres as a taste masking agent in fast disintegrating formulation, using highly bitter ambroxol hydrochloride as model drug.

MATERIALS AND METHODS:

Materials: Ambroxol hydrochloride was kindly donated by Tablets India Ltd, Chennai, India. Rosin and ethyl cellulose (10 cps) were purchased from S.D. Fine Chem., Mumbai, India. Microcrystalline cellulose (MCC) was purchased from FMC Biopolymer, PI, USA. Liquid paraffin, absolute alcohol, mannitol,n-hexane, Span-80 were purchased from Merck India Ltd, Mumbai, India. All other chemicals and reagents are of analytical grade. Double distilled water was used throughout the study.

Preparation and Characterization of Rosin: Ethyl cellulose Films:

1. **Free Film Preparation:** Films of the various ratios of rosin: ethyl cellulose (%w/v)such as 10:1,10:2,1:10,and 1:20 were prepared on a mercury substrate by solvent evaporation technique [13]. Both the polymers were dissolved in absolute alcohol and poured into a petridish containing mercury, allowing the solvent to completely evaporate for 48 hr and subsequently air drying for an additional 24 hr. The films were stored in desiccators at ambient temperature for 24 hr before they were studied (area of casting: 15 cm^2; approximate film thickness after drying 275 μm).

2. **Film Characterization:** Individual films from various ratios were cut into strips (10x10cm) and thickness was measured using a micrometer screw gauge. The tensile strength, percentage elongation at break of films and modulus of elasticity (Young's Modulus) were determined using an Instron Instrument (Model 4467, Instron Corp., Canton, MA) based on the standard ASTM test method [14]. The measurements were made at gauge length of 75 mm with crosshead speed (CHS) of 25 mm/min. The test was performed at 75% relative humidity (RH) at 25^{o}C using saturated solution of sodium chloride. The percentage elongation at break, E_b, of tested films was determined as follows ;

$$E_b = [E/L_o] \times 100$$

where, E is the extension to break of the film and L_o is its original length. The tensile strength, B, of tested films was determined using the following equation [15]:

$$B = F/A$$

where, F is the break force of the film and A is its crossectional area. The modulus of elasticity (Y) of the film was calculated from Hook's law [16]:

$$B = Y/[E/L_o]$$

The tensile strength, percentage elongation and modulus of elasticity of selected ratio was compared with standard taste masking polymer, Eudragit® E-PO in Table 1. All the results were reported as the mean (±S.D) of five replicates.

3. **Water Vapour Transmission Rate Studies:** Films of appropriate dimensions (1x1cm) was mounted on a charged cell containing saturated salt solution of sodium chloride to provide RH conditions of 75%, respectively [17-18]. The charged cells were weighed and placed in the desiccators containing anhydrous calcium chloride (0% RH). The cells were removed and reweighed every 24 hr intervals for 14 days. The amount of water transmitted through the film was given by the weight loss of the assembled cell. The rate of water vapour transmission was calculated using Utsumi's equation, Q = WL/S where W is water transmitted (g/24 hr), L is film thickness, S is surface area (cm^2), Q is water vapor transmission (g cm/cm^2/24hr) [19].

Preparation and Evaluation of Microspheres:

1. **Preparation of Microspheres:** Rosin and ethyl cellulose (10:1) finely grounded in a mortar and passed through sieve no.120 was used for the preparation of polymeric solution in absolute alcohol. Various concentrations of ambroxol hydrochloride were dispersed into this to obtain different ratios viz 1:1,1:2,1:4,1:7 and 1:10. It was then emulsified into an external light liquid paraffin phase containing 1 ml of 0.01%w/v of Span-80 solution to prevent the aggregation of microspheres. The mixtures was then stirred at constant stirring speed (3000 rpm) at room temperature for 30 min.The prepared microspheres were collected by decantation, washed with n-hexane to remove excess of liquid paraffin from microsphere surface and dried in an oven at 40°C for 5 hours.

2. **Estimation of Drug Loading:** An accurately weighed amount of microspheres were dispersed in alcohol and agitated in an orbital shaker until the microspheres were completely dissolved. The aliquot sample was filtered through membrane filter (0.2 µm Millex syringe driven filter unit, Millipore Corporation, Bedford, MA, USA) and diluted with distilled water. The drug content was determined spectrophotometrically at the wavelength of 245 nm using the linear (R^2 =0.99) equation y = 0.0244x + 00052. The drug content was expressed as the amount of drug encapsulated in a unit weight of microspheres. The drug content of each sample was determined in triplicate and results were averaged.

3. **Determination of Size and Size Distribution:** Laser diffraction (Malvern Instruments Ltd. Malvern, UK) was used to determine specific surface area, surface weighted mean, volume weighted mean and mean particle size. The size and size distribution of the microspheres were determined from a total of 100 microspheres of 10 cycles. The dispersant used was cyclohexane. Particle size and shape parameters like surface weighted mean D [3, 2], volume weighted mean D [4, 3], specific surface area were determined. Particle size distribution parameters like d (0.1), d (0.5), and d (0.9) were also analyzed. All the results were reported in Table 2 as the mean (±S.D) of five replicates.

4. **Surface Morphology Studies:** Scanning electron microscopy (SEM) was used to determine the surface morphology of the prepared microspheres. The microsphere was mounted on an aluminum stud using double adhesive carbon tape. Microspheres were coated using "POLORON"E5100 SEM, coating system. Scanning was done using LEO Electron microscopy Ltd, Cambridge; UK. The micrographs were recorded at HT 15 KV accelerating voltage using LEO 435VP.

FTIR and Differential Scanning Calorimetry Studies: Drug-polymer compatibility was studied using Fourier transform infrared spectroscopy (Perkin-Elmer, USA). Spectra of rosin, ambroxol, microspheres (drug-polymer ratio of 1:7) and physical mixture were recorded. Differential scanning calorimetry (DSC) was performed on microspheres, pure drug, placebo

microspheres and the drug loaded micospheres. DSC measurements were done with a DSC-60 instrument (Shimadzu, Japan). Samples were sealed in an aluminium pan and heated at a temperature range of 0-250^{o}C at the rate of 10^{o}C/min using indium as reference.

Preparation and Evaluation of Fast Disintegrating Tablets:

1. **Preparation of Fast Disintegrating Tablets:** The fast dissolving granulation consists of 75:25 physical mixture of MCC and mannitol respectively. All the ingredients as given in Table 5 were mixed and compressed in a single stroke tablet punching machine with 10 mm flat round punch at a fixed compression force. The punches and die were lubricated with magnesium stearate using a cotton swab preceding compression. The tablets were stored at 25°C and 34% relative humidity for one week in a desiccator. The relative humidity of the desiccator was controlled by the use of a saturated solution of magnesium chloride hexahydrate.

2. **Tablet Disintegration Studies:** Disintegration time was determined using the disintegration apparatus USP (Electrolab, Mumbai, India) in distilled water maintaining the temperature at 37±0.5^{o}C.

3. ***In vitro* Dissolution Studies:** *In vitro* dissolution was carried out (fast disintegrating tablets, immediate release tablets and rosin microspheres) in 900 ml phosphate buffer (pH 7.4) at 37±0.5^{o}C in a dissolution tester USP XXIV with a paddle rotation at 50 rpm [20]. An aliquot (10 ml) dissolution medium was withdrawn at various time intervals, filtered (0.2 µm Millex syringe driven filter unit, Millipore Corporation, Bedford, MA, USA) and absorbance was measured at 245 nm spectrophotometrically. An equal volume of the dissolution medium was added to the dissolution flask to maintain sink condition. The linear equation y = 0.0232x + 0003 was used to calculate amount dissolved at various time intervals.

4. **Sensory Study:** Sensory study was carried out on taste making, mouth feel attributes like grittiness, chalkiness, and overall preference, in healthy male volunteers who were emotionally and physically stable (Approved by Institutional Hospital Ethical Committee PA/356). Taste evaluation began immediately after oral administration of 500 mg of fast disintegrating tablets and continued for 60 sec. The taste masking period was expressed as the difference between the administration time and onset time of bitter taste as described by Al-Omran *et al* [21]. The subjects (n=5) were asked to record the time for the tablet to completely dissolve in the mouth and give scores for mouth feel attributes and overall liking of the product. Ranking is as follows. 1=best, 2=good, 3=satisfactory, 4=worst.

5. **Data Analysis:** Statistical analysis was performed by one-way analysis of variance (ANOVA) and t-test to test the effects of various treatments.

RESULTS AND DISCUSSION:

1. **Mechanical Characterization of Prepared Films:** The mechanical properties of free films are useful to assess the basic film forming properties of new materials, thereby predicting their usefulness for pharmaceutical coating and drug delivery. The polymer concentration, solvent system and presence or absence of plasticizers are important variables. A clear polymer solution was obtained with organic solvents like dichloromethane. Films of the different strengths of rosin: ethyl cellulose such as 10:1, 10:2, 20:1, 1:10 and 2:20 were prepared on a mercury substrate by solvent evaporation technique.

   Less than 2%w/v of ethyl cellulose resulted in rosin films which are brittle and non-flexible. Increasing the concentration above 2%w/v resulted in migration and deposition of polymeric material to the periphery of the film. The resulting films non-homogenous, visually showed an irregular distribution of polymer, assessed by varying thickness at different points. Based on the properties of the different ratio strengths prepared films, we have selected rosin: ethyl cellulose 10:2 (%w/v) for further evaluation. Films produced from the plasticizer free solutions containing the polymer were homogenous, smooth and translucent but slightly brittle.PEG 400 containing polymer films are soft, elastic, tough, therefore fulfill the desirable characteristics of a film former.

The results obtained in plastic tensile tests of free films are shown in **Table 1**. It is seen from the results that the tensile strength and modulus of elasticity of prepared films are lower compared to standard Eudragit L-100®. The percentage elongation of the prepared films is very high compared to the standard polymer, suggesting that the prepared polymers form films have all the desirable attributes of a film former.

TABLE 1: MECHANICAL PROPERTIES OF FREE FILMS

Mechanical Property	Rosin: Ethyl cellulose (10:1) (average±S.D)	Eudragit® E-PO (15%w/v) (average±S.D)
Thickness (µm)	275 (0.24)	195 (0.14)
Tensile strength (MN/m^2)	9.76 (0.45)	11.76 (0.65)
Elongation (%)	37.87 (15.12)	5.87 (1.32)
Modulus of elasticity (MN/m^2)	12.5 (0.18)	35.143 (12.89)

2. **Surface Morphology and Water Vapour Transmission Rate:** Scanning electron micrograph had shown that prepared films are smooth and uniform. Moisture absorption of polymeric films affects both the mechanical properties and drug release pattern. Water vapour transmission rate is very low (5.12×10^{-10} g cm/cm^2/24 hr) compared to the standard polymer, Eudragit® E-PO. Moisture absorption capacities under different humidity conditions revealed that the moisture uptake is minimum due to their hydrophobic characters [22]. Such low values of WVTR for the free films of the prepared polymers are indicative of their moisture protective ability [23].

3. **Preparation and Evaluation of Composite Microspheres:** Composite microspheres were prepared by emulsion solvent evaporation technique using different concentration of drug: polymer (1:1, 1:2, 1:4, 1:7 and 1:10).

The influence of concentration of polymer on the particle size was determined and was recorded in **Table 2**. It was found that particle size was minimum with 1:7 ratio. The encapsulation efficiencies with various ratios of drug and polymer were found to be in the range of 70-95%.

The data observed in **Table 3** indicated that the encapsulation efficiency increase with the increase in polymer content up to 1:7 ratios ($P < 0.05$) and the encapsulation efficiency decreased when the ratio was further increased to 1:10. It is likely that the medium might be saturated with polymer chains which could entangle and hinder encapsulation process therefore decrease the efficiency. As highest encapsulation efficiency was observed in microspheres prepared using the drug: rosin ratio of 1:7. Therefore, subsequent studies were carried out on the microspheres prepared using the same drug: polymer ratio.

TABLE 2: EFFECT OF THE DIFFERENT DRUG: POLYMER RATIO ON THE PARTICLE SIZE OF COMPOSITE MICROSPHERES

Drug: polymer	Specific surface area (m^2/g)	Surface weighted mean D [3,2]	Volume weighted mean D [4,3]	Mean particle size, d (0.5) (µm ± S.D)
1:1	0.604	9.93	40.46	10.7± 0.98
1:2	0.238	25.16	103.31	22.37 ± 0.08
1:4	0.218	27.56	150.14	80.88 ± 0.97
1:7	0.053	112.19	302.19	90.83 ± 0.79
1:10	0.158	26.78	125.43	120.65± 0.39

TABLE 3: EFFECT OF POLYMER CONCENTRATION ON THE AMBROXOL HYDROCHLORIDE LOADING OF COMPOSITE MICROSPHERES

Drug: polymer	Theoretical drug loading (%) (average±S.D)	Actual drug loading (%) (average±S.D)	Encapsulation efficiency (%) (average±S.D)
1:1	50.0	38.38 ± 5.78	76.76 ± 4.67
1:2	33.33	26.59 ± 7.89	79.77 ± 3.67
1:4	20.0	17.87 ± 4.83	89.35 ± 3.78
1:7	12.5	11.90 ± 3.26	95.20 ± 3.98
1:10	9.09	6.09 ± 7.90	66.99 ± 5.41

4. **Drug-Polymer Compatibility Studies and Physical Characterization:** Drug polymer interaction and the chemical stability of ambroxol hydrochloride in rosin microparticles was studied by FT-IR. The spectra of ambroxol hydrochloride, rosin, physical mixture and microspheres (drug: polymer, 1:7) are depicted in **Fig. 1**. In case of pure rosin, the characteristic carbonyl stretching band due to carboxylic acid was observed at 2360 cm^{-1}. Ambroxol hydrochloride showed characteristic bands at 1629 cm^{-1} due to NH_2 bending vibration. When drug was incorporated into the composite microspheres the above bands are retained, indicating no interaction between rosin and drug. This was further confirmed by the retention of above band in physical mixtures as well.

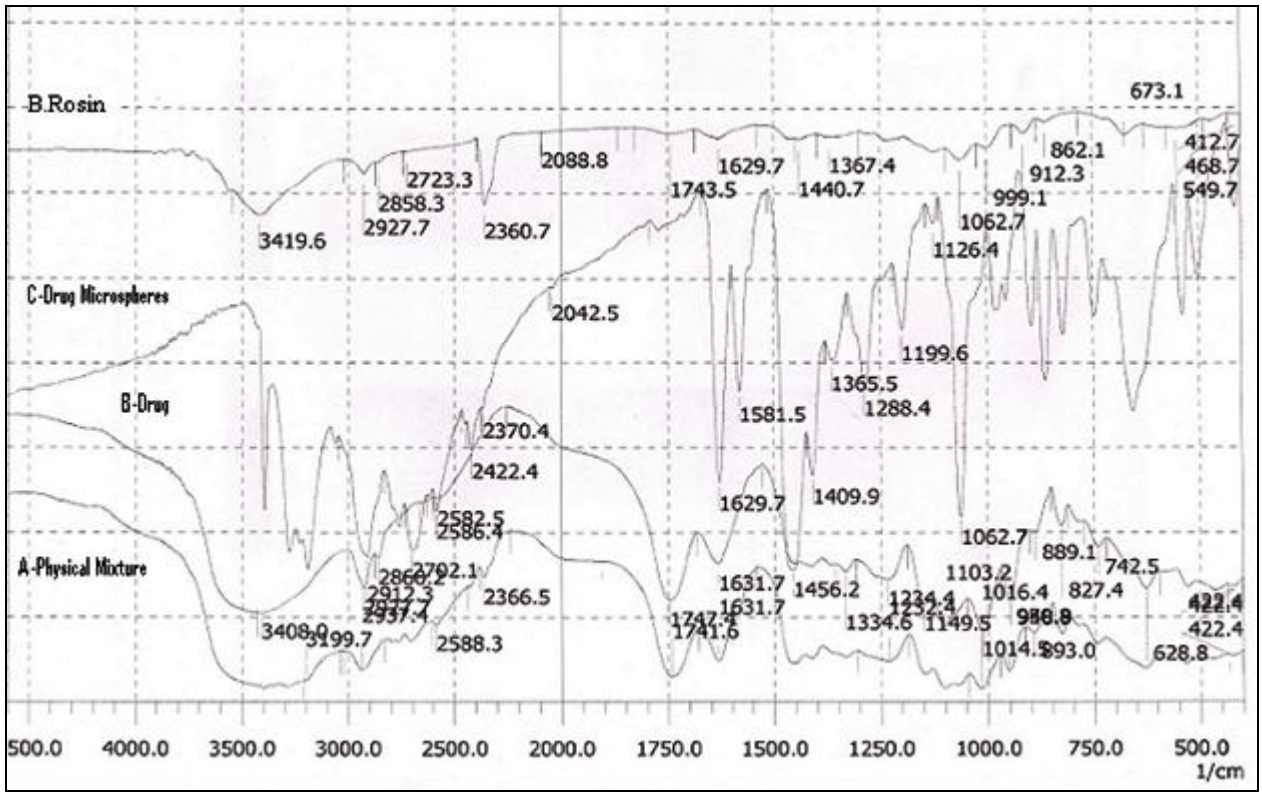
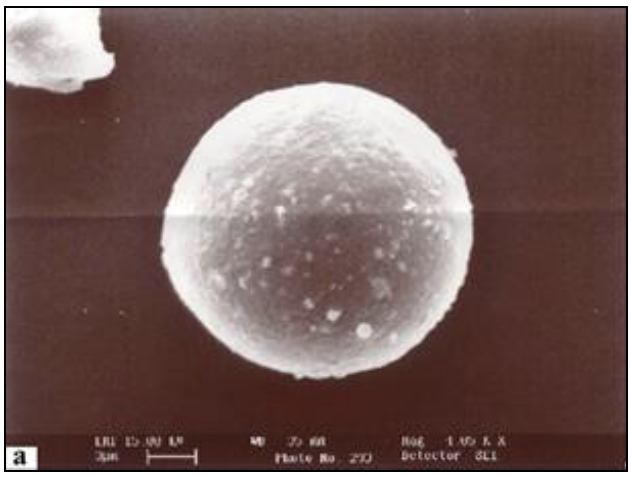


FIG. 1: FT-IR SPECTRA SHOWING ROSIN, PHYSICAL MIXTURE OF DRUG: ROSIN: ETHYL CELLULOSE (1:1:1), DRUG, DRUG MICROSPHERES, (DRUG: POLYMER 1:7) AND ROSIN

SEM photographs were taken for the composite microspheres prepared by emulsion solvent evaporation technique and are depicted in **Fig. 2**. The pictures revealed that the prepared rosin-ethyl cellulose microspheres were found to be smooth and spherical in shape. The physical state of the drug inside the microspheres was assessed by differential thermal analysis.



DSC thermograms of ambroxol, physical mixture of rosin and ethyl cellulose (1:1), blank microspheres and drug containing microspheres are shown in **Fig. 3**. Under the experimental conditions, no DSC peak was observed for the rosin and drug free microspheres. For the drug loaded microspheres the endotherm peak was similar to that of drug.

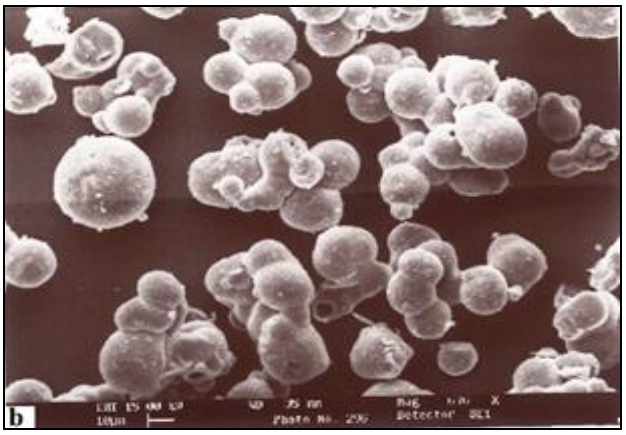


FIG. 2: SCANNING ELECTRON MICROGRAPH OF (a) SINGLE AND (b) GROUP OF COMPOSITE MICROSPHERES (DRUG: POLYMER 1:7) BY EMULSION SOLVENT EVAPORATION TECHNIQUE

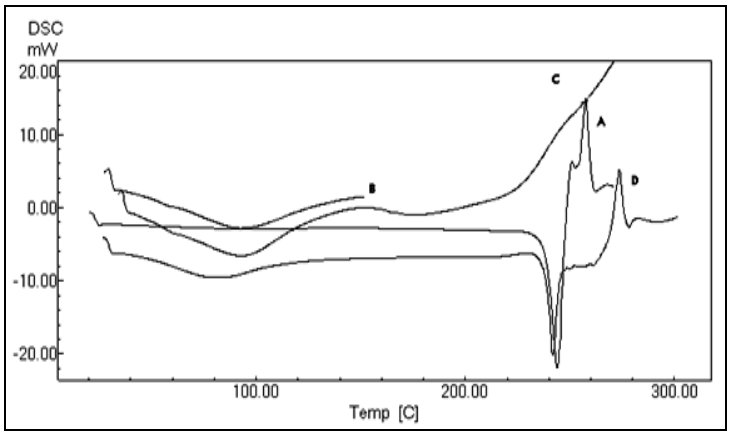


FIG. 3: DSC THERMOGRAMM OF (A) AMBROXOL HCL, (B) ROSIN, (C) BLANK MICROSPHERES AND (D) DRUG MICROSPHERES

5. **Preparation and *In vitro* Dissolution Studies Fast Disintegrating Tablets:** In the next stage, tablets were formulated using the prepared rosin microspheres using the composition mentioned in **Table 4**.

The disintegration time of the prepared fast disintegrating tablets (21.45 ± 05.30s) were found to be well within the defined limit of orodispersible tablets of BP 2009 [24]. *In vitro* dissolution studies were performed for the prepared microspheres, fast disintegrating tablets prepared using composite microspheres and commercially available immediate release tablet in phosphate buffer (pH 7.4) at 37 ± 0.5°C. It was apparent from **Fig. 4,** that the release profile obtained with the microspheres and its tablet dosage form (fast disintegrating) was comparable (P > 0.05) and the dissolution efficiency was higher when compared to the commercial available immediate release tablet.

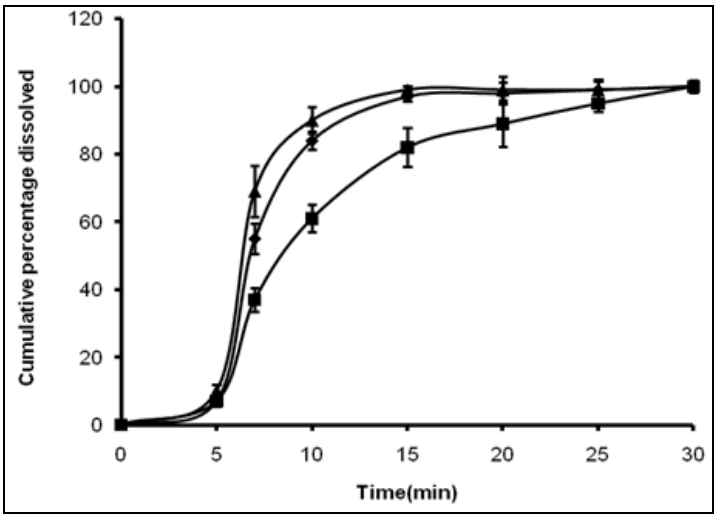


FIG. 4: DISSOLUTION PROFILE OF AMBROXOL HYDROCHLORIDE FROM DIFFERENT FORMULATIONS IN NEUTRAL MEDIA

Immediate Release Tablet, Composite Microspheres, Fast Disintegrating Tablets

TABLE 4: FORMULATION OF A FAST DISINTEGRATING TABLET PREPARED BY DIRECT COMPRESSION

Ingredients (mg)	Quantity (mg/tab)	Percentage (w/w)
Ambroxol hydrochloride microspheres (Equivalent to 30 mg of ambroxol HCl)	240.56	48.11
Crosscarmellose sodium	25.0	5.0
Corn starch	30.0	6.0
Aspartame sodium	9.5	1.9
American mint	3.5	0.7
Silicon dioxide	3.0	0.6
Magnesium stearate	2.1	0.42
Fast dissolving granulation	186.34	37.27

6. Analysis of the dissolution data at two time intervals like Q_{10} and Q_{20} (i.e., percentage of drug dissolved in 10 and 20 min respectively) reveals that dissolution rate decreased in the following pattern, rosin microspheres > fast disintegrating tablet > commercial immediate release tablet. The above data also revealed that the hydrophobic coating over ambroxol microspheres provides faster drug release. The amount of drug released was only eight percent in five minutes which could

sufficiently masked by flavoring and sweetening agent. The delay in drug release is long enough to pass through the oral cavity followed by fast and complete release as for any immediate release dosage form [25].

a. **Taste Masking Evaluation Studies:** Sensory study was carried out in five human volunteers and results have been shown in Table **5**.

The evaluation of the unpleasant taste of ambroxol hydrochloride revealed that the palatability and taste of the drug were significantly improved by the microencapsulation. This study suggests that prepared fast disintegrating tablets have a good overall preference score.

TABLE 5.SENSORY STUDY ON DISINTEGRATION TIME AND MOUTH FEEL ATTRIBUTES (RANKING ORDER: 1=BEST, 4=WORST)

Mouth feel attributes	Human Volunteers				
	V1	V2	V3	V4	V5
Disintegration time (s)	35	25	35	29	32
Grittiness	1	2	2	1	2
Chalkiness	2	2	2	2	2
Overall preference	2	2	3	2	2

Further, the dissolution profile obtained from the formulated fast disintegrating tablets shown that the release rate of ambroxol was not compromised by the tablets prepared using rosin loaded microspheres whereas it masked the bitterness of the drug. Thus the data observed in the current investigation suggests that modified natural polymer like rosin is an ideal polymer for taste masking the drugs and could be used for orally disintegrating solid dosage forms.

CONCLUSIONS: Composite microspheres containing ambroxol hydrochloride in micrometer size ranges were prepared successfully by w/o solvent evaporation technique, which was found to mask the taste of the drug significantly. The delay in drug release is only sufficiently long enough to pass through the oral cavity, followed by complete and immediate release in gastric fluid. Therefore, it is a viable option to include water soluble rosin coated drug in a fast dissolving dosage form. The ongoing investigations are in progress with viability of this combination to use it as an aqueous coating system.

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