ORIGINAL ARTICLE

A Comparative Study of Two Different Taste Masking Approaches for Taste Masking of Azithromycin

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Abstract

Objective: Azithromycin is a BCS Class II drug having a poor water solubility and bitter taste, which leads to poor patient compliance, especially in paediatric and geriatric patients. Thus in the present work taste masking was done using two methods, solid dispersion (SD) and complexation using ion exchange resin and the two methods were compared with respect to their efficiency of taste masking. **Methodology:** In this research work, SDs were prepared by solvent evaporation method using ethanol as a solvent. Furthermore, drug resin complex containing indion 234, a weak cation exchange resin was prepared by batch method. Both, SDs and drug resin complexes were evaluated by FTIR, SEM, PXRD, and DSC studies and with respect to their micromeritic properties, solubility, drug content, dissolution, and taste evaluation. **Results and Discussion:** The study showed that both the SDs as well as drug resin complex showed improvement in taste as well as physicochemical properties, The drug content and % drug release of the optimized batch prepared by SD method was found to be more that is 92.56 ± 0.75% and 96.77%, respectively for SD_5 (1:0.75) as compared to the optimized batch prepared by the ion exchange resin that is 67.52 ± 0.51% and 75.25% for DRC_4 (1:4).Taste evaluation studies also revealed a better taste masking with SD as compared to drug resin complex. Thus, it can be concluded that due to its versatile utility SD method was found to be the best and more efficient as compared to the ion exchange resin method for taste making of bitter tasting drugs.

Key words: Azithromycin, Bitter taste, Co-crystals, Taste masking

INTRODUCTION

Taste is an important parameter in administering drugs orally and governing compliance too.[1] It is a crucial factor that determines the palatability of pharmaceutical oral dosage form and patient compliance.[2] The oral administration of bitter drug is major concern for patient compliance. Several taste masking choices are accessible including sensory masking using correctives (flavors and sweeteners), chemical masking by chemical modification such as preparation of inclusion complex and prodrug by coating the particles surface, masking by using matrix and physical masking by additives. In case of pediatrics patients, unpleasant taste leads to noncompliance which decreases therapeutic efficacy.[3]

Different techniques have been tried and employed so far for taste masking such as addition of flavors and sweeteners,[4] microencapsulation,[5] prodrug approach,[6] crystallization,[7] inclusion complex.[8] Ion exchange resins,[9] and solid dispersion (SD) technique[10] are also widely used for this purpose.

Complexation using IERs is a simple, cost-effective technique requiring very less excipients in the formulation. IERs have excellent properties such as high ion-exchange capacity, good absorption capacity, physicochemical stability, and their insolubility in any solvents make them suitable candidates for the purpose of taste masking.[11]

IER are insoluble polymers which carry acidic or basic functional groups and that have the capability to exchange

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Received: 21-01-2021
Revised: 10-10-2021
Accepted: 03-11-2021

counter-ions within aqueous solutions surrounding them. An ion exchange resin is like a small bead with a diameter in between 1 and 2 mm. IERs can be used in a low concentration; they have a high drug loading capacity and drug resinates can be easily formulated into various dosage forms such as tablets and suspensions.[12]

SD is a unique approach which was introduced by Sekiguchi and Obi. They defined these systems as the dispersion of one or more active ingredient in an inert carrier matrix at solid state prepared by the melting (fusion), solvent or melting-solvent method. A number of freely water soluble materials such as citric acid, succinic acid, bile acids, sterols, and related compounds and polymers such as mannitol, urea, polyvinyl pyrrolidone, polyethylene glycols, and ß-Cyclodextrin used as carriers for SDs.[13] This approach is used to enhance the solubility and can also be used for the purpose of taste masking.[14]

Azithromycin (AZI), 9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin, a part of the azalide subclass of macrolides, is a broad-spectrum antibiotic with a long half-life and a high degree of tissue penetration.[15] It is primarily used for the treatment of respiratory, enteric and genitourinary infections. It is structurally related to erythromycin[16] and is a BCS Class II drug having a poor water solubility and an extremely bitter taste.[17]

In the present work, taste masking was done using two simple approaches namely SDs and complexation using IERs called as drug resin complexes (DRC). The SDs were prepared using carriers such as HPMC, mannitol and aspartame. For the purpose of complexation, a weak cation exchange resin Indion 934 which is chemically a high molecular weight crosslinked acrylic polymer,was selected The products so obtained were evaluated and compared to each other with respect to ease of formulation, taste masking efficiency, and product stability.

MATERIALS AND METHODS

Materials

AZI was received as gift samples from Ullman Laboratories, Aurangabad, India. Indion 234 was obtained as gift sample from Ion exchange resin house, Mumbai and Aspartame was procured from Stevfit sweeteners, Mumbai. All other chemicals were of standard grade procured from local suppliers.

Formulation of SDs of AZI

AZI taste masked SDs were prepared using solvent evaporation method.[18] Drug and carrier were taken in different ratios as shown in Table 1 and were dissolved separately in ethanol. The drug solution was then added to the carrier solution and stirred for few minutes. After entire dissolution, the solvent was evaporated at room temperature for 48 h. The solid mass is ground, sieved and dried and stored in a glass vials at room temperature.

Preparation of drug resin complex by ion exchange resin complexation method[19,20]

Purification of resin

Indion 234 was purified by washing with distilled water. Then, the wet resin was activated by 0.1M HCl followed by washing with distilled water. The resin was dried in oven at 60°C. The purified resin was stored in air tight glass vials.

Preparation of drug resin complex

The drug resin complex was prepared by batch method. AZI was mixed with Indion 234 in drug: Resin ratio of 1:1, 1:2, 1:3 and 1:4 as shown in Table 2. Distilled water was added to the mixtures and stirred with magnetic stirrer to allow complete complexation of drug with resin. The drug resin complex so obtained was filtered, residue was rewashed with distilled water. The prepared resinate was dried in oven at 60°C and stored in glass vials.

Characterization of formulation

Solubility studies

To determine the aqueous solubility of AZI, saturation solubility studies were carried out.[21] Saturation solubility studies were performed in distilled water in triplicate according to the method reported by Higuchi and Connors. Excess of AZI was added to 20 ml of distilled water taken in screw cap tube and shaken for 24 h in rotary flask at a room temperature to achieve the equilibrium. Appropriate aliquots were then withdrawn and filtered through Whatman filter paper no. 41 and analyzed spectrophotometrically at 284 nm. The results obtained from saturation solubility studies were statistically validated.

Determination of drug content

Drug content was determined by dissolving samples of SDs and DRC equivalent to 20 mg of AZI in ethanol and the volume was adjusted with distilled water.[20] The solution was filtered through Whatman filter paper no. 41, suitably diluted and absorbance was measured at 284 nm using double beam UV spectrophotometer (Shimadzu 1800, Japan).

Micromeritic studies

The flow properties of pure AZI, SDs and DRC was determined in terms of bulk density, tapped density, Carr's index, Hausner's ratio, and angle of repose.[22]

Dissolution studies

The dissolution studies were conducted in 900 ml of buffer (pH 6.8) at 100 rpm maintained at 37 ± 0.5°C in

Table 1: Composition of formulations of SDs

Ingredients (in grams)	SD_1	SD_2	SD_3	SD_4	SD_5
(Drug: Carrier)	(1:0.25)	(1:0.375)	(1:0.5)	(1:0.625)	(1:0.75)
AZI	1	1	1	1	1
HPMC	0.25	0.375	0.5	0.625	0.75
Aspartame	0.25	0.375	0.5	0.625	0.75
Mannitol	0.25	0.375	0.5	0.625	0.75
Ethanol (ml)	Qs	Qs	Qs	Qs	Qs

*AZI: Azithromycin, SDs: Solid dispersions. SD1, SD2, SD3, SD4, SD5: Formulation batches which are prepared by (Drug: Carrier) ratio

Table 2: Composition of formulation of DRC

Ingredients (in mg)	DRC_1	DRC_2	DRC_3	DRC_4
Drug: Resin	(1:1)	(1:2)	(1:3)	(1:4)
AZI	100	100	100	100
Indion 234	100	200	300	400

DRC: Drug resin complexes

USP dissolution apparatus I.[23] Weight of DRCs and SDs equivalent to 100 mg of AZI was added to dissolution medium and the samples were withdrawn at appropriate time intervals. The samples were immediately filtered through 0.45µm membrane filter, suitably diluted and analysed spectrophotometrically at 284 nm. The data obtained from dissolution studies were statistically validated.

Taste evaluation

Taste evaluation were done by time intensity method.[24] In this method, 10 healthy human volunteers were trained for taste evaluation. One mg of AZI was held in the mouth for 10 s and then spit out. In a similar manner SDs (1 mg) and DRC (1 mg) were held in the mouth until it was completely soluble. Bitterness was recorded against pure drug using a numerical scale.

Other evaluation parameters

Fourier transform infrared spectroscopy (FTIR)

FTIR spectra were obtained using a Shimadzu FTIR spectrometer (IR Affinity 1 Model, Japan) spectrometer. The samples of pure drug AZI, SD_5 and DRC_4were prepared into KBr disks. The scanning was kept from 400 to 500cm^{-1}.

Differential scanning calorimetery (DSC)

DSC of pure drug AZI,SD_5 and DRC_4 was done using a Shimadzu DSC 60 TSW 60 (Japan). Accurately, weighed samples were crimped in aluminum pans and heated from 36 to 500°C at a heating rate of 15°C/min in air atmosphere. An empty sealed aluminum pan was used as reference.

Powder X-ray diffraction

The X-RD data were recorded on a Philips Analytic X-Ray PW 3710 (Philips, Almelo. The Netherlands) diffractometer with tube anode Cr over the interval 10–70°/20 under the following sets of conditions: The generator (voltage) 45 kV and generator current: 25 mA.

Scanning electron microscopy (SEM)

The surface morphological properties of pure drug AZI, SD_5 and DRC_4were investigated by SEM-Jeol Instruments, JSM-6510, Japan. Samples were mounted on a double-faced adhesive tape, sputted with gold. Scanning electron photographs were taken at an accelerating voltage of and obtained micrographs were examined at 1024 × 768 magnifications.

RESULTS AND DISCUSSION

Formulation of SDs of AZI

The SDs of AZI were prepared using carrier in the ratio as shown in Table 1.

Preparation of drug resin complex

The DRC prepared by combining the drug and the rein Indion234 in different ratios as shown in Table 2.

Solubility studies

AZI shows poor aqueous solubility (8.40 µg/ml). Both and drug resin complexation method showed a significant improvement in the aqueous solubility of AZI as shown in Table 3, with SD_5 showing aqueous solubility as high as 91.26 ± 0.19µg/ml. Thus, it could be concluded that SDs proved to be better in terms of solubility improvement of AZI as compared to DRC.

Determination of drug content

Drug contents in SDs and DRC are shown in Table 3. SDs showed a good drug entrapment as compared to DRC with SD_4 showing a drug content of 92.56 ± 0.75%.

Micromeritic properties

The micromeritic properties of the SDs and DRC are as shown in Table 4. Both SDs and DRC exhibited better

micromeritic properties as compared to AZI. There is a marked improvement in the micromeritic characteristics of DRC in contrast to SDs, with DRC_2 giving the best result.

Dissolution studies

The dissolution curves of pure AZI alone and SDs and DRC are shown in Figures 1and 2, respectively.

The *in vitro* release of all the five batches of SDs showed a marked increase in the drug release pattern. In the first 10 mins, drug release was 48%, 44.11%, 50.13%, 58.33% 62.00% was for batches SD_1, SD_2, SD_3, SD_4, SD_5, respectively. The *in vitro* dissolution performance of SDs which was significantly higher in SD_5 batch than the plain drug that is 96.77%.

The *in vitro* release of all the four batches of drug resin complex showed a marked increase in the drug release pattern. The first 10 min, drug release was 16.29%, 18.67%, 21%, 23.41%, 29% for batch DRC_1, DRC_2, DRC_3, DRC_4 respectively. The *in vitro* dissolution performance of drug resin complex which was significantly higher in DRC_4 batch than the plain drug that is 75.25%.

Table 3: Saturation solubility and drug content of SDs and DRC

S. No.	Formulations	Solubility* (µg/ml)	% Drug Content *(w/w)
1.	AZI	8.40±0.06	---------
2.	SD_1	56.37±0.13	61.80±0.06
3.	SD_2	72.33±0.25	68.42±0.25
4.	SD_3	81.32±0.16	78.96±0.37
5.	SD_4	87.20±0.27	86.23±0.55
6.	SD_5	91.26±0.19	92.56±0.75
7.	DRC_1	23.11±0.011	48.51±0.08
8.	DRC_2	47.28±0.03	54.31±0.24
9.	DRC_3	68.34±0.23	60.49±0.48
10.	DRC_4	74.36±0.06	67.52±0.51

SDs: Solid dispersions, DRC: Drug resin complexes. Mean±SD, *n=3. SD: Standard deviation

Sensory evaluation

The taste evaluation scores of the SDs were carried out by making use of 10 healthy human volunteers. The ratings were done according to the bitter tasting scale which is as follows. The results are shown in Figure 3.

0 = Pleasant; 1 = Tasteless; 2 = Not bitter after taste gives bitterness; 3 = Immediately gives bitterness; 4 = Slightly bitter; 5 = Extremely bitter.

AZI shows extremely bitter taste whereas SD_5 and DRC_4 showed 0 and 1 taste evaluation rating, respectively.

Based on all these studies, we optimized SD_5 batch of SD and DRC_4 batch of drug resin complex and selected them for the further studies.

Other evaluation parameters

FTIR

Pure AZI spectrum shows sharp characteristics peaks at 355.88, 1032.93, 1050.29, 1064.04, 1124.55 cm^{-1}. The intensity of characteristic peak of drug was found to be reduced in case of the SD_5 and DRC_4which shows the molecular dispersion of drug. There was no considerable change in the position of characteristics absorption bands and bonds of various functional groups present in the drug. In case of SD_5 there is a shifting of peaks observed at 512.05, 635.71, 678.08, 705.01, and 1019.42. The shifting of peaks as in SD_5 and reduction in peak intensity as in DRC_4 indicate interaction between the drug, polymer, and resin [Figure 4].

Table 4: Micromeritic studies of SDs and DRC

S. No.	Formulations	Bulk density*(g/cc)	Tapped density*(g/cc)	Carr's index* (%)	Hausner's ratio*(%)	Angle of repose*(Θº)
1.	AZI	0.51±0.65	0.58±0.43	18.25±0.15	1.39±0.01	38.52±0.25
2.	SD_1	0.42±0.48	0.56±0.24	21.53±0.18	1.36±0.03	37.33±0.30
3.	SD_2	0.46±0.65	0.43±0.75	17.36±0.19	1.21±0.08	35.44±0.08
4.	SD_3	0.44±0.49	0.55±0.69	16.90±0.24	1.34±0.01	36.21±0.26
5.	SD_4	0.46±0.85	0.57±0.19	12.31±0.99	1.28±0.07	34.37±0.24
6.	SD_5	0.41±0.29	0.56±0.24	15.10±0.34	1.09±0.01	37.61±0.24
7.	DRC_1	0.43±0.14	0.52±0.21	16.40±0.11	1.29±0.40	30.82±0.89
8.	DRC_2	0.46±0.20	0.55±0.18	13.85±0.09	1.26±0.65	27.16±0.18
9.	DRC_3	0.49±0.19	0.57±0.26	15.98±0.21	1.19±0.43	31.94±0.05
10.	DRC_4	0.52±0.021	0.61±0.19	13.42±0.19	1.16±0.24	28.22±0.08

SDs: Solid dispersions, DRC: Drug resin complexes. Mean±SD, *n=3. SD: Standard deviation

DSC

The DSC thermographs of pure drug, polymer, resin, SD_5 and DRC_4 are shown in Figure 5.

Sharp endothermic peak value of AZI was obtained at 119.40°C.In case of SD_5 two sharp endothermic peaks of 110.71°C and 157.63°C were obtained which indicates a crystalline nature and in case of $DRC_4$the downward peak was not sharp but it was spread over a range of temperature.[25] These changes in DSC thermograms of $SD_5$and DRC_4were indicative of interactions that have occurred between drug and polymer and drug and resin resulting in formation of SD and drug resin complex, respectively.

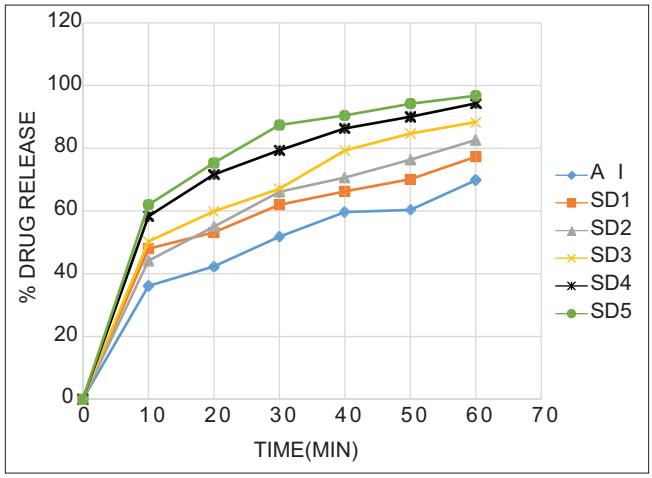

Figure 1: Dissolution studies of Solid dispersions

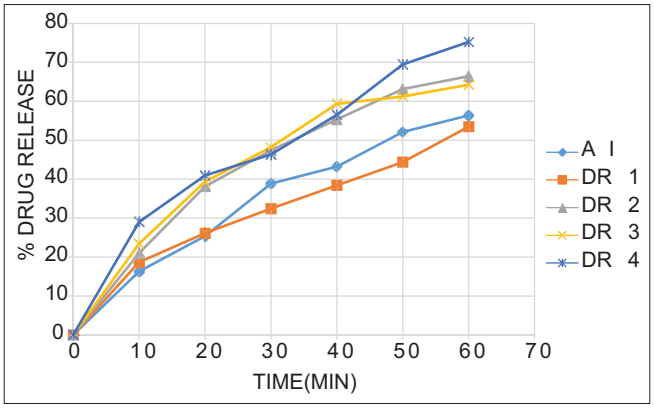

Figure 2: Dissolution studies of drug resin complex

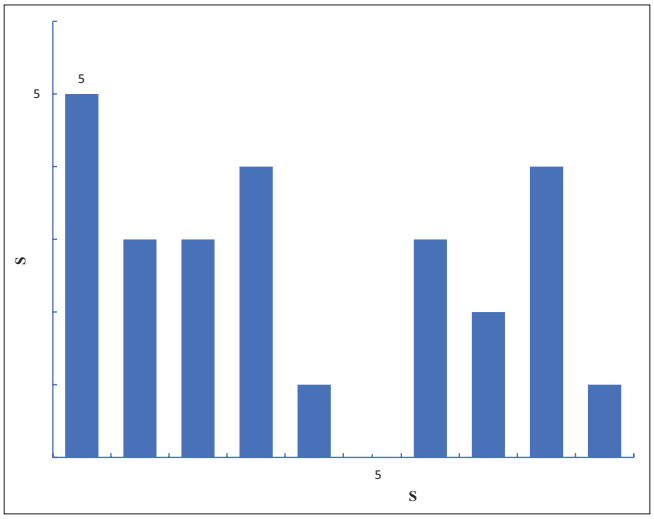

Figure 3: Taste Evaluation Scores of pure drug and solid dispersions

X-ray powder diffraction

XRD patterns of pure drug, SD_5 and DRC_4 are shown in Figure 6. XRD is a powerful technique for determining the

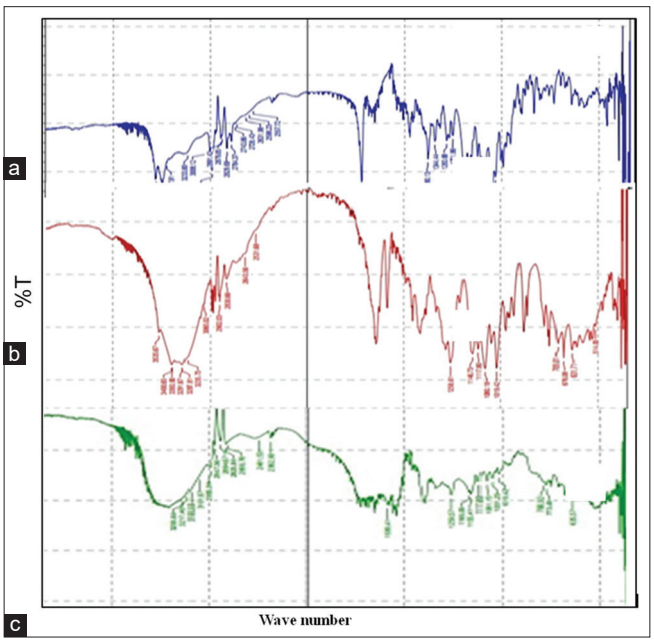

Figure 4: IR spectra of (a) AZI, (b) SD5, (c) DRC4

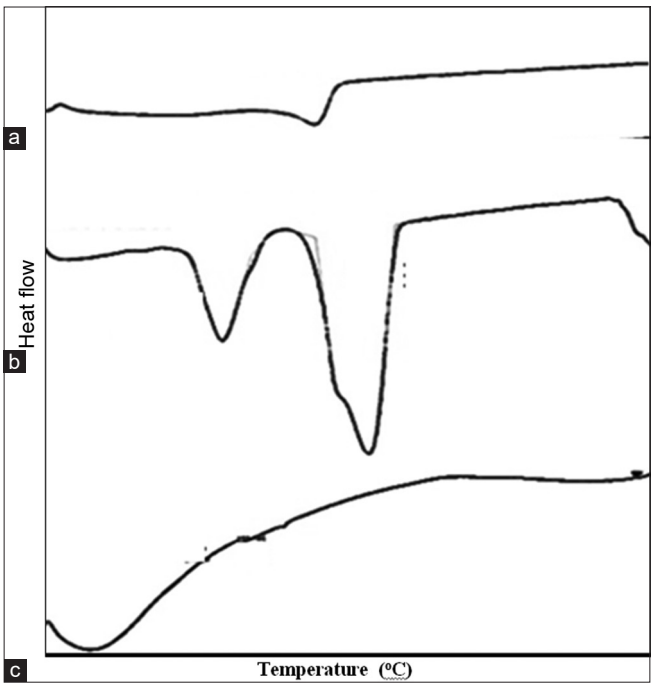

Figure 5: DSC (a) AZI, (b) SD5, (c) DRC4

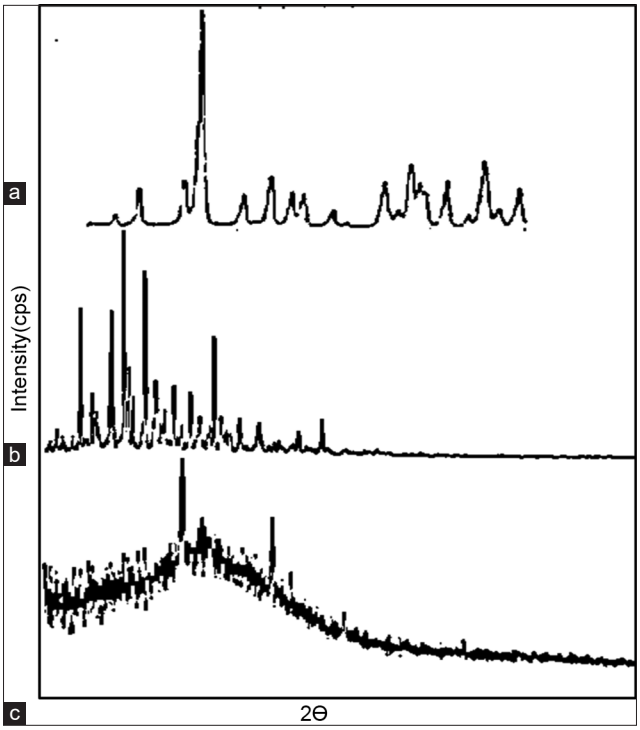

Figure 6: PXRD (a) AZI, (b) SD5, (c) DRC4

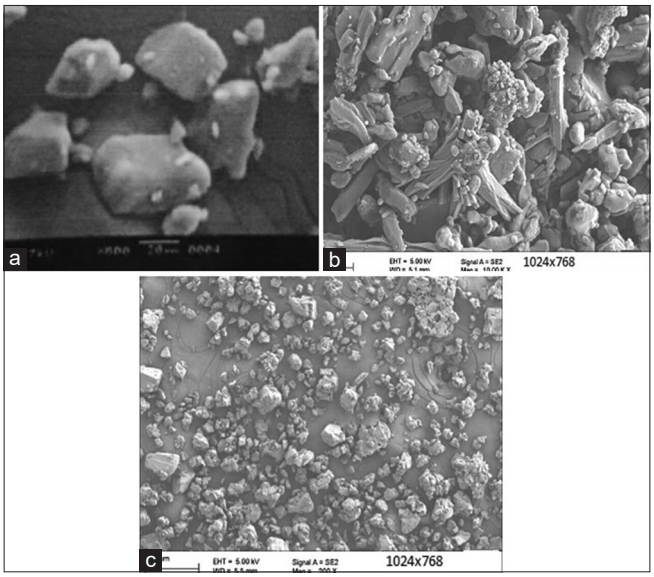

Figure 7: SEM (a) AZI, (b) SD5, (c) DRC4

crystal structure of unknown materials and to measure the size, shape, and internal stress of small crystalline regions. It can be seen that the optimized SD_5 and DRC_4 exhibits spectra with different peak positions (patterns) from the drug. The X-ray pattern thus obtained was found with the varying intensities with scattering angles and form very diffused peaks. From the literature, it is evident that such type of X-ray diffraction pattern can be observed with amorphous solids. Hence, it can be concluded that the X-ray diffraction of SD_5 shows it's crystalline nature due to presence of sharp peaks whereas X-ray diffraction of DRC_4 shows that it is amorphous nature due to the presence of diffused peaks.[26]

SEM

SEM of drug, SD_5 and DRC_4 are shown in Figure 7. Absence of crystalline structure in SEM images of AZI indicates its amorphous nature. Whereas, SEM images of SD_5 shows rod shaped crystalline structures and DRC_4shows presence of irregular aggregates which conforms that $DRC_4$is amorphous in nature.

CONCLUSIONS

Thus, in the present study, attempt has been made to prepare taste masked formulation of bitter drug AZI using solvent evaporation and ion exchange resin complexation method. For this purpose, SDs of the drug AZI were prepared using a combination of HPMC, Mannitol and Aspastame and DRC were prepared using a weak cation exchange resin Indion 234. The prepared SD s showed a marked improvement in taste, solubility and drug content as compared to the ion exchange resin method. The % drug release of the optimized batch prepared by SD method was found to be more that is 96.77% for SD_5 (1:0.75) as compared to the optimized batch prepared by the ion exchange resin that is 75.25% for DRC_4 (1:4). Thus, it can be concluded that due to its versatile utility SD method was found to be the best and more efficient as compared to the ion exchange resin method for taste making of bitter tasting drugs.

ACKNOWLEDGMENT

My heartfelt thanks to principal sir Dr. D. R. Chaple sir for making us available all the facilities in the college. I am thankful to Ullman Laboratories, Aurangabad for providing the drug sample of AZI and Ion Exchange Resin House, Mumbai, for providing the Indion 234.

CONFLICT OF INTEREST

None.

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Source of Support: Nil. **Conflicts of Interest:** None declared.