Inclusion of Amiloride Hydrochloride in Microporous Accurel MP 1000: Effect of solvents, drug loading and in vitro release

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ABSTRACT

The project was aimed at development of amiloride hydrochloride adsorbates using microporous accurel MP1000 to achieve controlled release floating system of highly water soluble drug. Of the four different methods used for preparing drug loaded adsorbates the method, stirring followed by vacuum using dichloromethane as the drug loading solvent was optimized after pharmacotechnical evaluation of the adsorbates (A1-A16). The polarity of solvent used for drug loading, drug loading methodology and surface properties of the adsorbent demonstrated crucial effect on adsorption and therefore on the release of drug from the porous carrier. Adsorbate A15 demonstrated highest drug content, maximum drug release and highest zeta potential ($\zeta = 2.92$). A15 was characterized for solid state analysis by DSC, FTIR, SEM and PXRD and the studies revealed physical deposition of drug crystals in the micropores of adsorbent without chemical interaction. The optimized adsorbate when developed into a directly compressible tablet resulted in a formulation that exhibited zero order release ($r^2 = 0.9985$) of highly water soluble drug and remain floated for 6 hr. Dissolution of drug was realised as the main mechanism of drug release.

Keywords: amiloride hydrochloride, accurel MP 1000, adsorbates, pharmacotechnical evaluation, in vitro drug release.

INTRODUCTION

Crystalline porous materials are emerging as a new category of host/guest systems. These materials possess vast amounts of pores that allow the inclusion of drugs in them [1]. These features allow them to adsorb drugs and release them in a more reproducible and predictable manner. Therefore use of mesoporous, microporous and nanoporous carriers used for drug delivery is a part of growing research [2-4]. Currently microporous materials find applications primarily as shape or size selective adsorbents because these possess several alternatives features such as stable uniform porous structure, high surface area, tunable pore sizes with narrow distribution and well defined surface properties [5]. Narrow pore size distribution permits selective entry of molecules into its pores and rejects molecules that are either too large or have a shape that does not match with the shape of the pore [6]. Close proximity of walls of micropores enhances the adsorption at low pressure as well.

Owing to wide range of useful properties, porous carriers have been used in pharmaceuticals for many purposes including development of novel drug delivery systems such as floating drug delivery system, sustained drug delivery system and improvement of solubility of poorly soluble drugs [7-11]. In the present study, polypropylene foam powder (Accurel MP 1000), owing to the following structural and adsorptive features, has been explored to modulate the release of highly water soluble model drug amiloride hydrochloride. Accurel MP 1000 is highly porous...
and hydrophobic having open cell structure, particle size less than 1500 µm, pore size in the range from 5-20 µm, void volume of 70% and very limited desorption. The solvent characteristics, drug loading methodology and surface properties of the adsorbent play important roles in the adsorption and therefore on the release of drug from the porous carrier. Therefore four different methods using four different solvents of varying polarity were selected for preparation of amiloride hydrochloride accurel adsorbates to understand the impact of experimental variations on the drug release.

Amiloride HCl, a salt of a moderately strong base (pKa 8.7) is designated chemically as 3,5-diamino-6-chloro-N-(diaminomethylene) pyrazinecarboxamide monohydrochloride, dehydrate [12] is an antikaliuretic-diuretic agent used for the treatment of diuretic-induced hypokalemia, primary and secondary hyperaldosteronism, edema, hypertension, congestive heart failure, polycystic ovary syndrome and female hirsutism [13]. Amiloride hydrochloride (AH) with low bioavailability of 15-25% is incompletely absorbed from the GI tract leading to fluctuations in plasma levels [14] with onset of action initiating not before 2 hr after an oral dose. Its effect on electrolyte excretion reaches a peak between 6 and 10 hr and lasts about 24 hr. Peak plasma levels are obtained in 3 to 4 hr and the plasma half-life varies from 6 to 9 hr. The fluctuations in plasma levels can be overcome by appropriate modulated release formulation. Thus the aim of the investigation was to design a floating controlled release formulation of a highly water soluble drug amiloride hydrochloride using the advantage of adsorbing capacity and low density of accurel MP1000.

MATERIALS AND METHODS

Materials
Accurel MP 1000 was purchased from Membrana (Germany), amiloride hydrochloride was purchased from Panacea Biotech (Chandigarh, India). Starcap 1500 was received as a gift sample from Colorcon Asia Ltd. (New Delhi, India). Methanol, ethanol, dichloromethane (DCM) and dimethylsulfoxide (DMSO) and other reagents were of analytical grade.

Methods
Preparation of AH loaded adsorbates
Amiloride hydrochloride was adsorbed on to Accurel MP 1000 by four different methods: stirring followed by solvent evaporation at room temperature (Method I), stirring followed by solvent evaporation at 40°C (Method II), vacuum loading (Method III) and stirring followed by vacuum (Method IV), using various loading solvents: methanol, ethanol, DCM and DMSO in each method to form adsorbates.

Method I: Accurately weighed amount (100 mg) of AH was dissolved in the methanol, ethanol (95%), DCM and DMSO separately. 900 mg of Accurel MP 1000 was incorporated slowly and mixture was stirred continuously using magnetic stirrer (SM Scientific Instruments (P) Limited, Delhi, India) at room temperature until the solvent was evaporated. The adsorbates (A1-A4) obtained were stored in desiccators until use.

Method II: Accurately weighed amount of AH (100 mg) was dissolved in the solvent methanol, ethanol, DCM and DMSO separately. Accurel MP 1000 (900 mg) was added slowly to the drug solution and stirred continuously using magnetic stirrer (SM Scientific Instruments (P) Limited, Delhi, India) at room temperature until the solvent was evaporated. The adsorbates (A5-A8) were stored in desiccators until use.

Method III [11]: Accurately weighed accurel MP 1000 (900 mg) was placed in a solution of the drug in methanol, ethanol, DCM and DMSO separately. The mixture(s) was evacuated for 1 hour using rotary vacuum evaporator (HICON, Grover Enterprises, New Delhi, India) after which the vacuum was released. The adsorbent and drug solution were then allowed to stand for 1 hour. Following this the solids (A9-A12) were separated using Whatman filter paper # 44 and dried for 24 hours at 60°C.

Method IV [15]: AH (100 mg) and accurelMP1000 (900 mg) were mixed separately with loading solvents and stirred using magnetic stirrer for 6 hour followed by evaporation at room temperature. The obtained powder was dried in vacuum for 3 hr to ensure complete removal of the loading solvents to get (A13-A16). The experimental design for preparation of adsorbates has been compiled in Table 1.
Table 1. Experimental design for preparation of the adsorbates of amiloride hydrochloride on accurel MP1000 and the drug loading data of the adsorbates

<table>
<thead>
<tr>
<th>Adsorbate Code</th>
<th>Drug (g)</th>
<th>Adsorbent (g)</th>
<th>Method</th>
<th>Percent drug loading ± S.D.</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>100</td>
<td>900 Methanol</td>
<td>-</td>
<td>82.80 ± 0.10</td>
</tr>
<tr>
<td>A2</td>
<td>100</td>
<td>900 Ethanol</td>
<td>-</td>
<td>84.30 ± 0.15</td>
</tr>
<tr>
<td>A3</td>
<td>100</td>
<td>900 DCM</td>
<td>-</td>
<td>92.69 ± 0.21</td>
</tr>
<tr>
<td>A4</td>
<td>100</td>
<td>900 DMSO</td>
<td>-</td>
<td>65.20 ± 0.06</td>
</tr>
<tr>
<td>A5</td>
<td>100</td>
<td>900 Methanol</td>
<td>-</td>
<td>86.40 ± 0.10</td>
</tr>
<tr>
<td>A6</td>
<td>100</td>
<td>900 Ethanol</td>
<td>-</td>
<td>87.30 ± 0.11</td>
</tr>
<tr>
<td>A7</td>
<td>100</td>
<td>900 DCM</td>
<td>-</td>
<td>93.16 ± 0.20</td>
</tr>
<tr>
<td>A8</td>
<td>100</td>
<td>900 DMSO</td>
<td>-</td>
<td>71.96 ± 0.15</td>
</tr>
<tr>
<td>A9</td>
<td>100</td>
<td>900 Methanol</td>
<td>-</td>
<td>85.00 ± 0.25</td>
</tr>
<tr>
<td>A10</td>
<td>100</td>
<td>900 Ethanol</td>
<td>-</td>
<td>89.10 ± 0.36</td>
</tr>
<tr>
<td>A11</td>
<td>100</td>
<td>900 DCM</td>
<td>-</td>
<td>92.26 ± 0.13</td>
</tr>
<tr>
<td>A12</td>
<td>100</td>
<td>900 DMSO</td>
<td>-</td>
<td>77.20 ± 0.17</td>
</tr>
<tr>
<td>A13</td>
<td>100</td>
<td>900 Methanol</td>
<td>-</td>
<td>85.50 ± 0.15</td>
</tr>
<tr>
<td>A14</td>
<td>100</td>
<td>900 Ethanol</td>
<td>-</td>
<td>91.50 ± 0.23</td>
</tr>
<tr>
<td>A15</td>
<td>100</td>
<td>900 DCM</td>
<td>-</td>
<td>97.07 ± 0.06</td>
</tr>
<tr>
<td>A16</td>
<td>100</td>
<td>900 DMSO</td>
<td>-</td>
<td>80.17 ± 0.15</td>
</tr>
</tbody>
</table>

Evaluation of the Adsorbates

Drug loading

Drug loading of AH loaded adsorbates was determined by the extracting 10 mg of drug loaded adsorbates with 10 ml of 0.1 N HCl. After appropriate dilution the drug was assayed in triplicate by measurement of absorbance at 362 nm using UV- spectrophotometer (PharmaSpec 1700, Shimadzu, Japan).

In vitro drug release

The release studies of AH loaded adsorbates were carried out in phosphate buffer pH 2.5 at 37 ± 0.5°C using USP type I dissolution rate test apparatus (HICON, Grover Enterprises, New Delhi, India). The release study was done at 100 rpm at 37 ± 0.5°C. Samples were withdrawn from the vessel at appropriate time intervals were replaced with fresh media and analyzed spectrophotometrically at 362 nm. The data obtained from was fitted into various kinetics equations by PCP disso software 2.0V, Pune India to elucidate out the mechanism of AH release from the adsorbates. Based on the drug release profiles, adsorbate from each group based on method of preparation was selected.

Surface charge determination

Surface charge determination of AH, accurel MP 1000 and A7, A11 and A15 was accomplished using Zetasizer (nano ZS, Malvern instruments, Westborough, MA, USA). Helium- neon gas laser having an intensity of 4mw was the light source. The equipment was programmed to provide 18mm laser width. Electrophoretic mobility (µm/s) was measured using small volume disposable zeta cell and converted to zeta potential by in-built software.

Solid state analysis

Differential scanning calorimetry

DSC was performed on AH, accurel MP 1000 and A15 using Perkin-Elmer differential scanning calorimeter equipped with liquid nitrogen sub ambient accessory (Perkin-Elmer (Pyris diamond), Tokyo, Japan). The instrument was operated under nitrogen pure gas at a rate of 20 ml/ min. Samples were sealed in the alumina pans (TA instruments, Belgium) and heated at a scanning rate of 10°C/min from 20 to 400°C.

X-ray diffraction

The powder diffraction patterns of the samples were obtained using a Bruker AXS D8 Advance (Kyoto, Japan) diffractometer and Cu-Kα radiation. The powder samples were kept in glass holder cavity. The diffractograms were run at 2.5°C minute⁻¹ with a chart speed of 2⁰/2 cm per 20 scale in a range of 50-300°C with a scan step size of 0.02 and time per step of 0.50s. The X-ray diffraction patterns were recorded automatically using Cu Kα radiations (λ= 1.5405980 Å), a current of 30 mA, and a voltage of 40 kV.
Fourier transform infrared spectrophotometry
FTIR spectra of the samples was determined by the KBr pellet method using a FTIR (Jasco FT761 (SHIMADZU, Kyoto, Japan)) spectrophotometer in the range of 400 – 4000cm⁻¹. The number of scans was adjusted automatically as a function of sample concentration in the pellet.

Scanning Electron microscopy
SEM photographs of AH, accurel MP 1000 and selected adsorbate were obtained using a scanning electron microscope Leo- 435 VP, U.K. The samples were gold coated by sputter coater E5 100 UK Polaron for 15-20 minutes and the photomicrographs were taken under various magnifications depending on the sample.

Tableting and Evaluation
The adsorbates A7, A11 and A15 was subjected to direct compression by single punch electrically operated punching machine (Hicon, Grover enterprises, New Delhi, India), using 8-mm diameter, circular punches with flat faces. A quantity of adsorbates equivalent to 5 mg of AH with microcrystalline cellulose (5% by wt) as disintegrant and spray dried lactose IP (quantity sufficient) were geometrically mixed and lubricated with 1% by wt of magnesium stearate IP. The blend obtained was directly compressed to tablets of 100mg and evaluated for official (weight variation and disintegration test, IP 2007) and unofficial (fiability) tests for tablets. The tablets were also subjected to in vitro drug release test as described in earlier section. Additionally, the tablets were visualized by SEM pre- and post dissolution.

RESULTS AND DISCUSSION
Effect of experimental variables on preparation of adsorbates
The adsorbates (A1- A16) were prepared by four different methods and each method was accomplished using solvents of variable dielectric constant, viscosity and boiling point as shown in Table 2. The solvents used for preparation of adsorbates were methanol, ethanol (95%), DCM and DMSO. Appropriate selection of the solvent for the processing is documented to enhance the yield, or determine characteristics such as purity, and solubility. Therefore, the solvent may appear be a critical parameter in the formulative process. DCM and methanol belong to class II category of ICH Q3C (R4) section [15] are associated with less severe toxicity and exhibit no potential adverse effects. Ethanol and DMSO on the other hand belong to class III category of ICH Q3C(R4) section that lists the solvents with low toxic potential to man and no health based exposure limit is needed. Thus, the use of these solvents was considered safe for preparation of adsorbates and these were stored in dessicator for sufficient period to ensure complete removal in Drug loading was estimated in all adsorbates and is tabulated in Table 1. The drug loading was highest (80.17% - 97.07%) in adsorbates prepared by method IV probably due to use of vacuum coupled with stirring used in the preparation. Both the process variables augmented the loading as stirring caused the disturbance of stagnant saturated layer of drug around the accurel particle and setting up of concentration gradient for adsorption on to the particle and application of vacuum helped in displacement of air with in the porous structure of accurel by the solution of drug. Thus the drug gets adsorbed within the pores and on to the surface resulting in high drug loading. The effect of stirring on drug loading in method IV was clearly visible when compared to method III that used vacuum as the sole loading technique and thus resulted in lower drug loading (77.2% - 92.26%) in comparison to method IV. Further drug loading by use of method II (71.96% - 93.16%) was less than method III but higher than method I (65.20 – 92.71%). Both, method I and method II were accomplished by stirring of adsorbent and drug solution followed by solvent evaporation. The difference used in the methods based on solvent evaporation was the temperature used for evaporation. In method I evaporation was accomplished at room temperature (25°C) whereas solvent was evaporated at 40°C in method II. The difference in quantum of drug loading can be attributed to the difference in temperature used that affected the physical properties of the solvent, more significantly the viscosity of solvents used for drug loading. An increase in temperature decreased the viscosity of solvent hence faster migration of solute on the adsorbent. Conclusively vacuum coupled with stirring were identified as advantageous processing factors for high drug loading onto porous adsorbent.

Apart from the method used for drug loading, the physical properties of the solvent (Table 2) also had significant effect on drug loading. DMSO with highest viscosity exhibited least drug loading (65.20% - 80.17%) in all the methods (Table 1) whereas highest drug loading (92.71% - 97.07%) was observed when DCM with least viscosity of 0.437 was used as loading solvent. In addition to viscosity, the effect of dielectric constant was also identifiable.
Table 2. A compilation of physical properties of the solvents used for the preparation of Amiloride hydrochloride-accurel MP 1000 adsorbates

<table>
<thead>
<tr>
<th>Solvents</th>
<th>Dielectric constant</th>
<th>Viscosity (poise)</th>
<th>Boiling point (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMSO</td>
<td>47.2</td>
<td>2.14</td>
<td>189</td>
</tr>
<tr>
<td>Methanol</td>
<td>33.62</td>
<td>0.544</td>
<td>64.46</td>
</tr>
<tr>
<td>Ethanol (95%)</td>
<td>24.3</td>
<td>1.074</td>
<td>78.29</td>
</tr>
<tr>
<td>DCM</td>
<td>9.08</td>
<td>0.437</td>
<td>40</td>
</tr>
</tbody>
</table>

DCM of least dielectric constant (9.08) and low boiling point (40°C) facilitated migration of the drug molecules [16] and resulted in highest drug loading. This is quite in contrast to least drug loading documented with methanol of highest dielectric constant of 33.62. In fact low dielectric constant promotes interactive behaviour of solute molecules with hydrophobic polypropylene surface that has been reported by other researchers as well [2,8].

**In vitro release**

The release of AH from the adsorbates (Fig. 1) varied with the method and type of solvent used for adsorption. Distinctly, the adsorbates made with DCM showed higher cumulative percent drug release in comparison to those made with other solvents. Predominantly, the release of the drug is governed by the release of molecules from the porous network of accurel connected to the surface [17]. Additionally, the pore geometry, physical and chemical interactions with the matrix walls of the adsorbent can also contribute to the release [18].

![Fig.1. In-vitro release profiles of adsorbates in phosphate buffer, pH 2.5](image)

When a porous hydrophobic polymeric drug delivery system is placed in contact with the appropriate dissolution medium, release of drug to the medium is by either the drug dissolution in the water filled pores or from the surface or by diffusion through the water filled channels. As reported in literature the overall drug release from the porous carrier is governed predominately by either diffusion or dissolution or both, which in turn are also influenced by the amount and solubility of the drug [9]. In our case the drug being highly soluble, dissolution appears predominant mechanism of drug release.

Quantitative analysis of drug release profiles documented highest %CDR from the adsorbates prepared by the method IV (a maximum of 94.75% from A15) and the least CDR was observed with adsorbates prepared by method I (A1-A4). Apparently the highest drug loading documented with adsorbates prepared by method IV was the simple reason for higher release than other groups. In each group, the adsorbates prepared using DCM as the loading solvent (A3, A7, A11 and A15) displayed highest %CDR at the end of dissolution. DCM with low boiling point, low dielectric constant and less polar nature is reported to cause fast transformation of the phase [19] than other solvents, that in turn affected higher drug release. Adsorbates prepared by method I released the drug at slowest rate.
and hence were discarded. Thus further studies were continued with A7, A11 and A15. It is relevant to specify that the adsorbates remain floated for 6 hr during the in vitro release study in the simulated fed state medium, phosphate buffer, pH 2.5.

Surface charge on adsorbates
Investigations were carried out to estimate the surface charge of the AH loaded adsorbates A7, A11 and A15. Drug loading on adsorbents can affect the surface charge of the latter that can consequently effect the aggregation of particles and hence the surface area available for release of drug. Thus estimation of surface charge was undertaken and Zeta potential (ζ) of accurel was estimated at -0.00129 (Table 3) that upon AH (ζ=1.66) loading changed in its magnitude and nature of charge. The magnitude of charge varied with the method used for preparation of adsorbates and was inversely related to conductivity. Highest zeta potential was documented for A15 (ζ = 2.92) prepared by method IV and the least for A11 (ζ = 0.0411) prepared by method III.

Table 3. Surface charge and conductivity data of amiloride hydrochloride, accurel MP 1000 and various selected adsorbates.

<table>
<thead>
<tr>
<th>Test substance</th>
<th>Zeta potential (mv)</th>
<th>Zeta Deviation</th>
<th>Conductivity</th>
<th>Method of drug loading</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiloride Hydrochloride</td>
<td>1.66</td>
<td>95.6</td>
<td>0.0121</td>
<td>-</td>
</tr>
<tr>
<td>Accurel MP 1000</td>
<td>-0.00129</td>
<td>10.7</td>
<td>0.00142</td>
<td>-</td>
</tr>
<tr>
<td>A7</td>
<td>1.50</td>
<td>16.0</td>
<td>0.00883</td>
<td>Method II</td>
</tr>
<tr>
<td>A11</td>
<td>0.0411</td>
<td>5.10</td>
<td>0.0246</td>
<td>Method III</td>
</tr>
<tr>
<td>A15</td>
<td>2.92</td>
<td>14.2</td>
<td>2.97e-4</td>
<td>Method IV</td>
</tr>
</tbody>
</table>

As discussed earlier drug loading was maximum when stirring was coupled with vacuum especially on the surface of adsorbent so was demonstrated by surface charge measurements. Thus maximum zeta potential was observed for A15. Zeta potential indicates degree of repulsion between adjacent similarly charged particles in dispersion and will resist aggregation. Conventionally, a high zeta potential can be high in positive or negative sense i.e. -30 mv or +30 mv would be considered as high zeta potential [20] but in this case the charge was considerably low enough to resist aggregation between the AH loaded adsorbates. This provided maximal surface area for drug release and hence %CDR was maximum for A15.

Fig. 2. Differential scanning calorimetry of amiloride hydrochloride, accurel MP1000 and adsorbate A15
Solid state analysis

For further understanding of the adsorption process solid state analysis studies were carried out. The thermograms exhibited sharp intense endothermic peak at 140°C and small broad endothermic peak at 320°C (Fig. 2) corresponding the melting point(s) of accurel and AH respectively [21,22]. DSC thermogram of A15 retained both the endothermic peaks at 140°C and 313.7°C suggestive of no chemical change taking place as a result of adsorption.

This was corroborated with powder X Ray diffraction studies. The diffractogram of AH (Fig 3a) and accurel (3b) showed numerous distinctive peaks that indicated crystalline nature of both. However the crystallographic pattern of A15 (3c) was essentially that of accurel with disappearance of peaks at (13.4°, 18.6°, 23. 5°) and retention of peaks at 11.58° and 17.60°. The diffractogram of AH almost completely merged within the diffractogram of accurel suggestive of adsorption of drug within the porous network of accurel.

As evidence to the proposed concept, scanning electron microscopy was performed. Electron micrographs of AH (Fig. 4a) showed the rod shaped crystals of amiloride hydrochloride whereas the microporous characteristics were displayed in Fig 4b. The scanning electron micrographs of A15 (Fig. 4c, d) evidenced small crystals of AH predominantly lodged within the micropores of AH and some surface deposition could also be seen. Crystals of AH were formed as a result of solvent evaporation and the surface of the adsorbent provided nucleation sites for crystallization. Within the pores, the surface available for nucleation was larger than on the periphery of pores, which resulted in greater deposition of AH crystals in the pores.
In order to assess the chemical interactive status between AH and accurel in the adsorbate, DRS studies were done. The DRS spectra of AH (Fig. 5) exhibited peaks at 3300 cm$^{-1}$ (-N-H), 1700 cm$^{-1}$ (-CO-NH), 1000 cm$^{-1}$ (-C-Cl), 1400 cm$^{-1}$ (-C=N) and 1300 cm$^{-1}$ (-C-N) [23].

The DRS spectra of accurel showed distinct peaks characteristic of the polypropylene polymer and the spectra of A15 was a cumulative spectrum of AH and accurel indicative of no chemical interaction occurring during adsorption of AH on accurel.
Fig. 5. Diffuse reflectance spectra of (a) adsorbate A15, (b) Accurel MP 1000 and (c) amiloride hydrochloride

Fig. 6. In-vitro drug release profiles of directly compressed tablets of adsorbates A7, A11 and A15 coded as F7, F11 and F15 in phosphate buffer, 2.5
Tableting and evaluation
Adsorbate A15, formulated as directly compressed tablet (F15) was subjected to in-vitro drug release studies in reference to the tablets of A7 and A11 coded as F7 and F11 respectively. As seen in the Fig.6 the %CDR was maximum form F15 followed by F7 and F11. The Fig.6. In-vitro drug release profiles of directly compressed tablets of adsorbates A7, A11 and A15 coded as F7, F11 and F15 in phosphate buffer, 2.5 release profile of AH from F15 was almost similar to A15. Presence of MCC, a multifunctional excipient facilitated disintegration of the tablet due to the capillary action that promoted easy wetting [24]. The release was also promoted by Starcap 1500 which is co-processed mixture of corn starch and pre-gelatinized starch commercially available as an inert free flowing, low dust excipient with disintegration and dissolution properties independent of media pH leading to consistent release profiles in vivo (25). The release profile of F15 best fitted zero order release ($r^2 = 0.9985$).

SEM of pre- and post dissolution of F15 was undertaken to visualize post dissolution changes in the formulated tablet. The SEM of pre-dissolution tablet showed cracks and fissures (Fig. 7a) that on magnification showed discrete deposits of amiloride hydrochloride (Fig. 7b).

Upon dissolution, interestingly the tablet remained intact in its shape but pores could be observed clearly (Fig. 7c) that was the skeleton of compressed accurel with scarce drug deposits within the pores (Fig. 7d). This is indicative of gradual dissolution of drug from the intact tablet matrix and the composition when suitably modified using release modifiers may serve as a platform for extended release of highly water soluble drugs.

**CONCLUSION**
Adsorbates of amiloride hydrochloride with maximum drug loading were successfully developed by optimizing the conditions for development. The adsorbate prepared by stirring of AH with accurel in DCM as drug loading solvent followed by vacuum drying resulted in an adsorbate with maximum drug loading. The selected adsorbate when developed into a directly compressible tablet resulted in a formulation that can provide zero order drug release.
REFERENCES