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localized in the lungs for up to 12 h in comparison to 6 mins for free \(^{99m}\text{Tc}\), indicating prolonged retention of the BDS liposomes in lungs (fig. 3). In vivo acute toxicity study indicated the safety of budesonide loaded liposomes. In the in vivo efficacy studies, recovery time after histamine challenge significantly reduced in liposome treated guinea pigs at all time points confirming the sustained action of liposomal BDS (fig. 4). In conclusion, this investigation led to the development of stable freeze dried liposomal systems for pulmonary delivery of budesonide. With this system, it was possible to obtain localized sustained action of drugs in lungs with marked reduction in toxic effects associated with the drug.

ACKNOWLEDGEMENTS

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REFERENCES


Generation of Budesonide Microparticles by Spray Drying Technology for Pulmonary Delivery

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Treating respiratory diseases with inhalers requires delivering sufficient drug to the lungs to bring about a therapeutic response. For optimal efficacy, drug administration must be reliable, reproducible and convenient. Enhanced powder dispersibility could be designed into microspheres and porous particles through a combination of novel formulation and process design. The present work outlines the design of dry powder inhaler (DPI) formulations to achieve delivery goals. Formulation development, characterization strategies and processing methods have been discussed. Budesonide (BUD) has wide range of inhibitory activities against inflammatory mediators. Conventional BUD DPI formulations were developed and the effect of various grades of inhalable lactose on respirable fraction was studied. BUD microspheres and porous particles were developed using spray drying technology which resulted in improved respirable fraction of BUD.

MATERIALS AND METHODS

Budesonide was obtained from Lupin Ltd., Mumbai; gelatin and chitosan were procured from SD Fine Chemicals, Mumbai and different grades of inhalable lactose were obtained as gift sample from DMV Int., The Netherlands.

Development of conventional BUD DPI formulations:
Drug was mixed with fine lactose and this premix was dispersed over coarse lactose in geometric proportions and developed formulations were characterized (Table 1). Degree of deacetylation of chitosan was determined by IR spectroscopy.

Development of microspheres and porous particles by spray drying:
Polymers chitosan, gelatin and their combination were spray dried using a Labultima Mini Spray Dryer. Process parameters were optimized using 2 factorial design. Effect of different parameters was studied (fig. 1). Gelatin /BUD and chitosan/ BUD were spray dried in water: methanol (1:1) as 1.0% and 0.5% w/v, respectively. Porous particles were generated by adding chloroform (5% v/v) as blowing agent. In vitro deposition was determined using a Twin Stage Impinger apparatus. Particles were also subjected to Anderson Cascade Impactor studies to determine mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD). DSC studies were performed.

In vitro release studies:
These studies were conducted using Flow Through Cell assembly (USP IV) at 37° with flow rate of 16 ml/min (in 100 ml of phosphate buffer pH 7.0). Five milliliter sample was analyzed by UV Spectrophotometry at 246 nm. Mechanism of drug release was determined using various kinetic models. Coefficient of correlation from plots of Q vs. t (cumulative % drug release vs. time), log Q vs. log t and Q vs. square root of t were calculated.

RESULTS AND DISCUSSION

BUD DPI formulations were developed using various grades of inhalable lactose like Pharmatose, Lactohale, Inhalac and mannitol in various combinations. The effect of particle size of excipients on respirable fraction of BUD was assessed (Table 1 and fig. 1). Degree of deacetylation of chitosan was found to be 45%. Optimum process parameters were inlet temperature (130°), aspirator rate (50%), feed
Microspheres and porous particles of BUD were prepared with chitosan (1:2, drug: polymer ratio) with 86% and 96% w/w entrapment efficiency, respectively.

Developed chitosan microspheres and porous particles were characterized for particle size (SEM analysis).

**TABLE 2: RESULTS OF OPTIMIZED DPI FORMULATIONS PREPARED BY SPRAY DRYING TECHNOLOGY**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>BUD microspheres</th>
<th>BUD porous particles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appearance</td>
<td>Hollow, porous</td>
<td>Hollow, porous, free flowing microspheres</td>
</tr>
<tr>
<td>Particle size</td>
<td>1-10 µm</td>
<td>1-10 µm</td>
</tr>
<tr>
<td>% yield</td>
<td>20-30</td>
<td>20-30</td>
</tr>
<tr>
<td>% moisture content</td>
<td>0.3770</td>
<td>0.3280</td>
</tr>
<tr>
<td>% drug entrapment</td>
<td>86.00 (RSD= 0.4890)</td>
<td>96.00 (RSD= 0.2616)</td>
</tr>
<tr>
<td>% FPF</td>
<td>35.6785%</td>
<td>46.8199%</td>
</tr>
<tr>
<td>MMAD</td>
<td>4.60 µm</td>
<td>4.30 µm</td>
</tr>
<tr>
<td>GSD</td>
<td>1.75 µm</td>
<td>2.54 µm</td>
</tr>
</tbody>
</table>

FPF is fine particle fraction; MMAD is mass median aerodynamic diameter and GSD is geometric standard deviation.

**Fig. 2: Factorial design for optimization of process parameters.**
(a) Effect of aspirator and feed spray pressure on % yield; (b) Effect of aspirator rate and feed spray pressure on % drug entrapment; (c) Effect of aspirator rate and inlet temperature on moisture content of product

**Fig. 3: SEM micrograph of developed formulations**
(a) Chitosan microspheres and (b) chitosan porous particles
Fig. 4: DSC spectra of developed formulations (a) BUD porous particles; (b) BUD microspheres; (c) BUD pure; (d) Chitosan pure; (e) BUD conventional formulation

TABLE 3: REGRESSION COEFFICIENTS FOR FORMULATIONS

<table>
<thead>
<tr>
<th>Formulations</th>
<th>Zero order</th>
<th>Korsmeyer-peppas</th>
<th>Matrix</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gelatin microspheres</td>
<td>0.4272</td>
<td>0.9920</td>
<td>0.9166</td>
</tr>
<tr>
<td>Chitosan microspheres</td>
<td>0.8338</td>
<td>0.9722</td>
<td>0.9898</td>
</tr>
<tr>
<td>Gelatin porous particles</td>
<td>1.0000</td>
<td>1.0000</td>
<td>1.0000</td>
</tr>
<tr>
<td>Chitosan porous particles</td>
<td>0.8315</td>
<td>0.9877</td>
<td>0.9906</td>
</tr>
</tbody>
</table>

- JSM- 840A/WDS/EDS Sys- JEOL instrument, fig. 3), % drug entrapment and % FPF (Table 2). DSC studies confirmed no interaction between drug and polymer (fig. 4). In vitro release profile is shown in fig. 5a. Regression coefficients (near to 1) for zero order, matrix and Korsmeyer-Peppas kinetic equations confirmed release by slow zero order kinetics through diffusion matrix (Table 3, fig. 5b and 5c). Korsmeyer-Peppas plot indicated good linearity ($r^2 = 0.9722$).

Microspheres and porous particles were engineered to be both hollow and porous and these exhibited excellent flow and dispersion from passive DPIs. In vitro characterization predicted highly efficient lung delivery. The results indicated that spray drying technology can be used to generate inhalable particles like microspheres and porous particles with improved pulmonary deposition as compared to conventional DPI formulations.

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Microemulsion of Lamotrigine for Nasal Delivery

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Epilepsy is a neurological disorder which requires quick management of seizures in order to avoid the risk of permanent brain damage. Intranasal administration allows transport of drugs to the brain circumventing BBB, thus providing a unique feature and better option to target drugs (for example lamotrigine) to the brain with quick onset of action in case of emergencies such as epilepsy. We have already reported microemulsion (ME) of lamotrigine for nasal delivery1. Further, previous studies on ME of tamoxifen citrate (hydrophobic drug) have demonstrated a dramatic increase in solubility with micellar and ME despite poor solubility of drug in oily phase2. This finding can be utilized in formulation of nasal ME of hydrophobic drugs. Improved solubilization by virtue of ME can exploited to accommodate higher drug concentration per unit nasal ME as nasal anatomy pose severe constraints on volume of formulation to be administered. This can aid reduction of dosage volume of nasal ME ultimately resulting in high patient compliance. The objective of present study was to evaluate the role of ME components in solubilization of lamotrigine. Ascertaining the role of ME components would create better understanding of the system for further formulation development.

MATERIALS AND METHODS

Formulation components are listed in Table 1 with equilibrium solubility data. ME and micelles (MI) were formulated using surfactant - cosurfactant mixtures, Solutol HS 15 and Transcutol P in the ratio of 1:2 and Solutol HS 15: soluphor P in the ratio of 1:1, with and without oil phases, respectively. Solubilization by ME and MI was determined by adding excess of lamotrigine and concentration of solubilized drug was determined by UV spectrophotometry (307 nm) after 48 h of equilibration.

RESULT AND DISCUSSION

The observed solubilization capacity of ME and MI systems was much lower than the predicted solubility calculated from the summation of contribution of each component of the system (Table 2). Furthermore the improvement in solubilization capacity of ME over MI was not high in relation to the equilibrium solubility data for lamotrigine in the three oil phases. Also the solubilization capacity of the ME did not increase with

| TABLE 1: FORMULATION COMPONENTS AND EQUILIBRIUM SOLUBILITY OF LAMOTRIGINE |
|-----------------------------|-----------------------------|
| Formulation components (mg/ml ± SE) | Lamotrigine solubility |
| Oily phases | |
| Capmul MCM | 45.13 ± 0.1821 |
| Peceol | 18.04 ± 0.3564 |
| Captex 355 | 0.93 ± 0.1245 |
| Peceol | 67.38 ± 0.685 |
| Captex 355 | 70.67 ± 0.7189 |
| Surfactant | |
| Solutol HS 15 | 133.39 ± 0.7726 |
| Solutol HS 15 | 13.46 ± 0.3834 |
| Co surfactants | |
| Transcutol P | 67.06 ± 0.7189 |
| Soluphor P | 133.39 ± 0.7726 |
| Soluphor P | 13.46 ± 0.3834 |
| Aqueous phase | |
| Water | 0.17 ± 0.678 |

| TABLE 2: COMPARISON OF PREDICTED AND OBSERVED SOLUBILIZATION CAPACITIES OF ME AND MI |
|-----------------------------|-----------------------------|
| Oil phase | Concentration of oily phase (% w/w) | Solubilization (mg/ml ± SE) | Solubilization capacity observed |
| Capmul MCM | 3.5 | 68.32 | 34.01±0.034 |
| 8.5 | 70.67 | 34.07±0.9596 |
| Peceol | 3.5 | 67.38 | 29.87±0.685 |
| 7 | 68.1 | 30.02±0.1555 |
| Captex 355 | 3.5 | 66.78 | 28.57±0.1619 |
| 5 | 66.79 | 28.55±0.448 |
| Micelles | - | 66.75 | 26.33±0.125 |

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