Pre-formulation Screening of Metered Dose Inhaler Using Molecular Dynamic Simulation Approach

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Introduction

- Due to environmental concerns, propellants considered the most challenging components in MDIs formulations.The first generation of MDIs used chloroflourocarbons (CFCs) as the propellant which phased out and replaced by Hydroflouroalkane (HFAs) with zero ozone layer depletion but significant global warming potential, so the industry is in the same situation of needing to find replacements to the existing HFA propellants with lower GWP alternatives.[1]
- The last 30 years has seen a major advances in computer simulation of chemical processes.
- For this proof-of-concept study, we chose the target of replacing ethanol with PEG400 at a concentration(1%) in formulation containing micronized salbutamol sulfate (SS) dispersed in HFA134a containing oleic acid and ethanol, which is necessary to dissolve the oleic acid and is responsible for unfavorable consequences like reduction of saturated vapour pressure.[2]
- Two potential substitute stabilizer were selected PVP k30 and Brij 72 and Molecular dynamic (MD) simulation depending on Florry Huggins's theory was used to predict the compatibility of suggested stabilizers with other formulation components such as PEG400 and SS before adding the HFA134a propellant.[3]
- The results were compared with Differential scanning calorimeter (DSC) results for the previous formulations. Ethanol free formulations were evaluated by determining the content per actuation during (0,3,6 months) at accelerated stability condition (40° C/75%RH).

Objectives

This paper addresses a question of whether computational modelling of MDI formulation can assist in the selection of excipients , thereby reducing the amount of physical trial and error investigation.

Methodology

PEG400(1%) was used as possible alternative cosolvents for ethanol. Brij72 and PVP-k30 were used as stabilizer with different concentration in preparing the suggested initial suspension based formulation free off ethanol. All formulation were prepared using fixed concentration of salbutamol sulfate and PEG400 as mentioned in table (1).

Table 1. Suggested formulation of S-Br, and S-Pv

Formulation	Components	Stabilizer type	Percentage (%)
S-Br	SS PEG400 Brij72	Brij72	0.001-0.005-0.01
S-Pv	SS PEG400 PVP-k30	PVP-k30	0.001- 0.0001

- Simulations were performed using Material Studio Blend Protocol to estimate calculated chi and Emix for S-Br and S-PV. Then, HFA134a was added and the suggested formulation were filled in 10 metal canisters and, separately, two poly ethylene terephthalate(PET) vials using a double-stage filling technique.
- Visual observation was used to aid selection of the optimum percentage of stabilizer.
- Initial Suspension of suggested formulations with optimum percentage of stabilizer were evaluated using DSC apparatus.
- Content per actuation for formulation that passed visual observation were evaluated experimentally under accelerated stability conditions at (40° C/75%RH).
- Four actuations were released into the air by priming the MDI and Ten actuations were collected into British Pharmacopeia sampling apparatus. The apparatus was rinsed with 11.5ml ammonium acetate buffer and 10ml methanol. The collected liquid was transferred to a graduated 50ml volumetric flask and methanol added to achieve a final volume of 50ml for subsequent analysis HPLC analysis.

Results

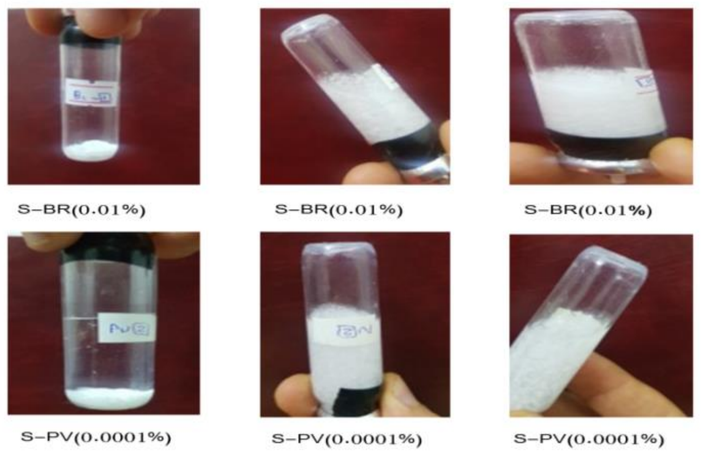
MD Simulation results:

χ and E_{mix} were calculated for the studied components at 298 K as shown in table 2. (negative values or approximately equal to zero are preferred).

Table 2. Chi parameter and mixing energy for the mixtures of S-Br and S-PV

Formulation	Components	Base – Screen	χ	Emix
S-Br	SS PEG400 Brij72	BRIJ72_SS	44.58	26.40
		BRIJ72_PEG400	48.43	28.68
S-Pv	SS PEG400 PVP-k30	PVP- K30_PEG400	**4.99**	**2.95**
		PVP- K30_SS	**-412.34**	**-244.18**

Visual Observation results:

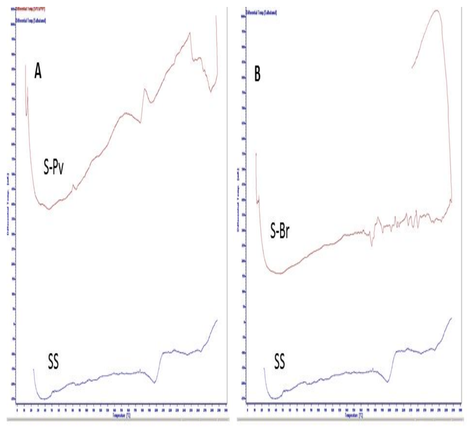


DSC results:

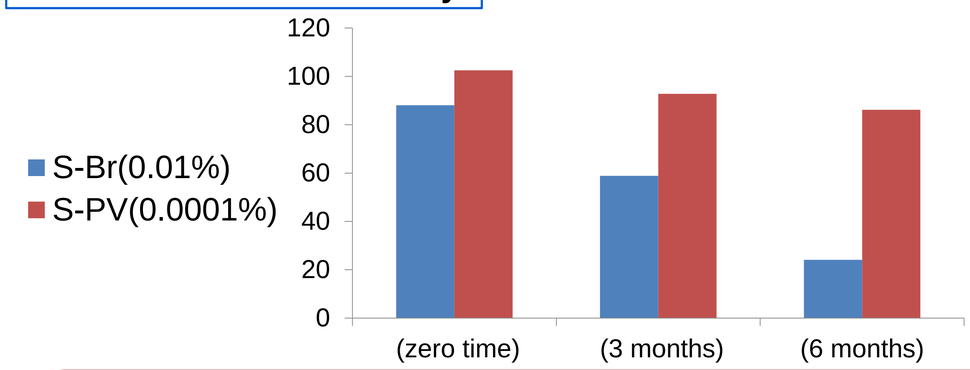
The endothermic maximum melting point was employed to assess compatibility in this work and the results are demonstrated in Table 3.

Table 3. Endothermic onset and maximum melting point of SS, S-Br and S-PV

Formulation	Endothermic onset melting point (°C)	Endothermic maximum melting point (°C)
SS	183.7	197.5
S-Pv(0.0001%)	189.5	199.5
S-Br(0.01%)	183.7	186.3



Content Per Actuation Assay:



Conclusion

According to the results the predicted , mixing energy, and chi parameter indicated that PVP-K30 compatibility with formulation components is higher than Brij72 and these results were confirmed by DSC thermograms. Content per actuation assay indicates that ethanol (10%) could be replaced by PEG400(1%) in presence of PVP-k30(0.0001%).

References

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