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Study of Polymorphism on Pargeverine Hydrochloride

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ABSTRACT

Objectives: Screening active pharmaceutical ingredients for polymorphs is of utmost importance in drug development to enable stable APIs, robust manufacturing processes and reduction of costs incurred in switching over crystal forms. The current study deals with exploring polymorphism in Pargeverine Hydrochloride using different solvents and solvent systems. **Methods:** Drug was crystallized by slow solvent evaporation of filtered saturated solution using either single or mixed solvent systems. The resultant crystals were evaluated for physical appearance and by Fourier-transform Infrared Spectroscopy, Differential Scanning Calorimetry and Powder X-Ray Diffraction. **Results:** The physical appearance, melting points, pattern of heat flow for phase transition, peak temperature and the IR spectra and Powder X-Ray Diffraction pattern of the crystals of Pargeverine Hydrochloride in single and mixed solvent systems (50 solvent systems) did not show any marked difference from that of pure drug. **Conclusion:** From the results, it can be concluded that there were minimal possibilities of polymorph formation for Pargeverine HCl in the solvent/s or combination of solvents attempted, thus need for any specific controls to inhibit transition during its routine manufacturing process may not be required.

Key words: Crystal, Mixed solvent systems, Pargeverine HCl, Polymorphs, Single solvent.

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INTRODUCTION

Crystal form plays a significant role in the Active Pharmaceutical Ingredient (API) of a drug product and thus screening for polymorphs of APIs is a common practice. If polymorph screening is not performed it may lead to potential problems like non-robust API manufacturing processes, unstable API, lack of information on solid forms; cost ridden need to switchover crystal forms well into drug development.[1]

Different crystal structures of polymorphs lead to variations in the molecular physical properties like molecular volume, molar volume, refractive index, density, hygroscopicity, solubility, electrical and thermal conductivity, crystal axis owing to variations in dimensions, symmetry, shape, capacity and void volumes. Varied Interactions between the elements in the crystal lattice and differences in packing lead to variability in melting points, surface free energy, kinetics, spectroscopic and mechanical properties between polymorphs affecting dissolution rates, compatibility, flow and blending properties.[2]

Polymorphs may have an impact on the drug product manufacturability owing to the differences in mechanical properties and crystal morphologies which affect the compressibility and the flow properties of the powder mixture.[3–5]

Experimentation has shown that the initial concentration, solvent, cooling rate, nucleation temperature and seeding strategy govern the nature of the polymorph.[6] However there is no theory established for solvent selection for solution crystallization. Further there is no clarity on the interactions between solvent and solute molecules and its impact on crystallization process and crystal properties.[7]

Pargeverine Hydrochloride, 2-(dimethyl amino) ethyl 2,2-diphenyl-2-prop-2-ynoxyacetate; hydrochloride [Figure 1] used as spasmolytic agent and is soluble in water, chloroform, methanol.

Review of literature indicates that no polymorph/s of Pargeverine Hydrochloride has been reported.

The objective of the study is to explore the possibilities of polymorph formation in Pargeverine Hydrochloride and its impact on physicochemical/pharmacological properties.

MATERIALS AND METHODS

Material and reagents

Pargeverine Hydrochloride was obtained as gift sample from M/S R L Fine Chemicals, Bangalore.

All the chemicals were of standard grade and used without further purification.

Instruments

The melting points of resultant crystals were determined by open tube capillary method and are uncorrected. FTIR spectra were recorded with IR AFFINITY 1S instrument. DSC analysis of selected samples was performed on a Pyris 6 DSC at Unichem Laboratories, Goa. PXRD pattern was obtained using Bruker advance diffractometer at Sanofi Synthelabo Development Centre, Goa.

Recrystallization

For crystallization from single solvent, the slow solvent evaporation method was used in which the material solution was kept standstill for a period of time on filtration at room temperature. A covering of Aluminum foil with a few holes served to control the rate of evaporation.

For multicomponent solvents, the second solvent was added to the saturated solution of the drug in the first solvent. Solubilization was facilitated by heat wherever required.[8]

RESULTS

The melting range of drug Pargeverine hydrochloride is 172-174°C. Table 1-2 gives the appearance and melting range of resultant crystals.

IR spectra of randomly selected resultant crystals S7, S9, M4, M7, M8 of Pargeverine Hydrochloride are presented in Figure 2-3.

DSC peak temperatures of crystals S1, S9, M7, M8, M9, M17 are presented in Table 3.

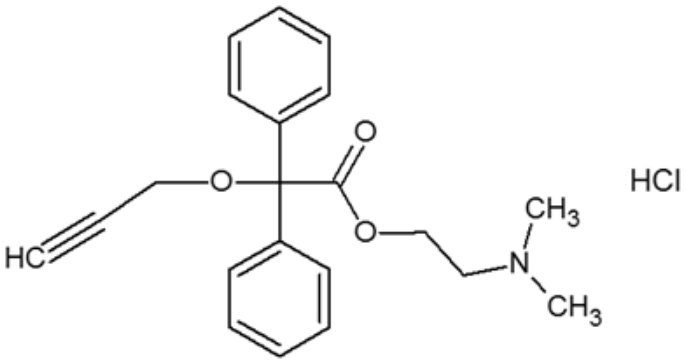

Figure 1: Chemical structure of pargeverine Hydrochloride.

Table 1: Physical appearance and melting range of Pargeverine Hydrochloride crystals from single solvent.

Sr. No.	Sample code	Solvent system	Physical appearance	Melting Range (°C)
1	S1	Isopropyl alcohol	White	171-174
2	S2	Ethanol	White	166-169
3	S4	Isobutanol	White	166-170
4	S5	Dichloromethane	White	168-170
5	S6	Chloroform	White	168-172
6	S7	Acetonitrile	White	169-170
7	S8	Acetone	White	166-171
8	S9	Methanol	White	170-174
9	S10	Methyl isobutyl ketone (MIK)	White	171-173
10	S11	1-Propanol	White	170-172
11	S12	Tert-butyl alcohol	White	162-166
12	S15	Methyl ethyl ketone (MEK)	White	168-170

Table 2: Physical appearance and melting range of Pargeverine hydrochloride crystals from mixed solvent systems.

Sr. No.	Sample code	Solvent system	Physical appearance	Melting Range (in °C)
1	M1	Ethanol: Acetonitrile 3:1	White	170-172
2	M2	Ethanol: Acetone 3:1	White	172-174
3	M3	Ethanol: Isopropyl alcohol 3:1	White	169-171
4	M4	Ethanol: n-butanol 3:1	White	170-172
5	M5	Ethanol: Isobutanol 3:1	White	170-172
6	M6	Ethanol: Dichloromethane 3:1	White	168-172
7	M7	Methanol: Acetonitrile 3:1	White	170-174
8	M8	Aqueous Methanol	White	170-172
9	M9	Methanol: Isopropyl alcohol 3:1	White	170-172
10	M10	Methanol: Acetone 3:1	White	167-170
11	M11	Methanol: n-butanol 3:1	White	172-174
12	M12	Methanol: Isobutanol 3:1	White	166-170
13	M13	Methanol: Dichloromethane 3:1	White	168-170
14	M14	Chloroform: Isopropyl alcohol 3:1	White	167-170
15	M15	Chloroform: Acetone 3:1	White	169-170
16	M16	Chloroform: n-butanol 3:1	White	168-170
17	M17	Chloroform: Isobutanol 3:1	White	169-172
18	M18	Chloroform: Dichloromethane 3:1	White	167-170
19	M19	Chloroform:Acetonitrile 3:1	White	166-171
20	M20	Aqueous Ethanol	White	166-169
21	M21	Methanol: Methyl isobutyl ketone 3:1	White	164-168
22	M22	Chloroform:Methyl isobutyl ketone 3:1	White	166-170
23	M23	Ethanol: Methyl isobutyl ketone 3:1	White	168-172

Table 2: Physical appearance and melting range of Pargeverine hydrochloride crystals from mixed solvent systems.

Sr. No.	Sample code	Solvent system	Physical appearance	Melting Range (in °C)
24	M24	Chloroform: Methyl ethyl ketone 3:1	White	172-174
25	M25	Chloroform:1-Propanol 3:1	White	171-174
26	M26	Isopropyl alcohol: Acetone 5:1	White	162-166
27	M27	Isopropyl alcohol : Acetonitrile 5:1	White	168-170
28	M28	Isopropyl alcohol : Dichloromethane 5:1	White	158-160
29	M29	Isopropyl alcohol : Methyl isobutyl ketone 5:1	White	172-174
30	M30	Isopropyl alcohol : Methyl ethyl ketone 5:1	White	158-162
31	M31	Acetone: Acetonitrile 5:1	White	172-176
32	M32	Acetone:1- propanol 5:1	White	170-172
33	M33	Methanol: Methyl ethyl ketone 5:1	White	170-172
34	M34	Isopropyl alcohol: N,N-Dimethylformamide 5:1	White	162-164
35	M35	Ethanol : Methyl ethyl ketone 5:1	White	162-166
36	M36	Acetone : Dichloromethane 5:1	White	166-168
37	M37	Acetone: N,N-Dimethylformamide 5:1	White	164-168
38	M38	Isopropyl alcohol: N,N-Dimethylacetamide 5:1	White	170-172

Table 3: DSC peak temperatures of crystals of Pargeverine Hydrochloride.

Sample code	DSC Peak Temperature (in °C)
Pure Drug	172.91
S1	173.23
S9	172.04
M7	174.15
M8	171.53
M9	172.97
M17	173.81

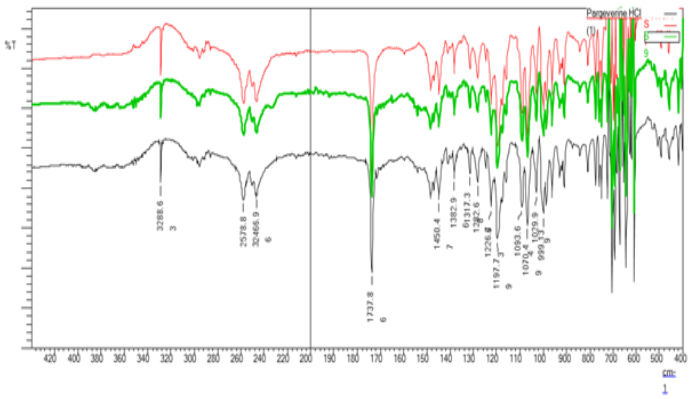

Figure 2: Overlay IR Spectra of Pargeverine Hydrochloride, S7 (Acetonitrile) and S9 (Methanol).

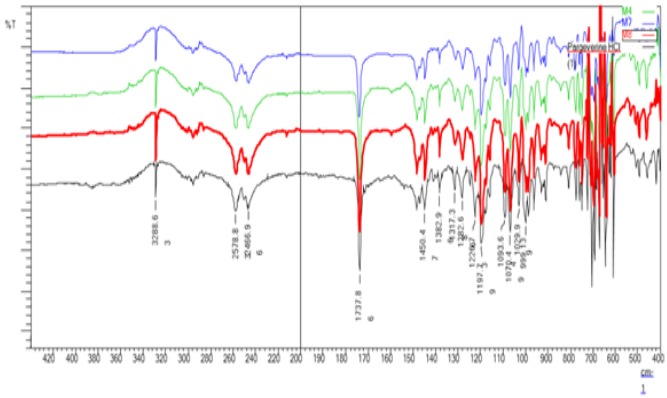

Figure 3: Overlay IR Spectra of Pargeverine Hydrochloride, M4 (Ethanol: n-butanol 3:1), M7 (Methanol: Acetonitrile 3:1) and M8 (Aqueous Methanol).

PXRD study was done on selected crystals and pattern obtained with rhombic crystals of M4, M17, M24 is compared with that of S9 in Figure 4.

DISCUSSION

Existence of polymorph forms could impact physico-chemical properties of a drug molecule altering its solubility, bioavailability and manufacturability. For e.g. for a drug like Carbamazepine under the Biopharmaceutical Classification system Class II (Low solubility / High permeability); the rate limiting factor is the solubility of the drug in the aqueous medium of the GIT. For such drugs, polymorphic forms with enhanced solubility in the aqueous medium will increase dissolution rates and thus drug bioavailability.[3,9,10] Also in case of Paracetamol, if no controls are placed to prevent transition, polymorphic Form II converts to Form I and its compressibility is lost thus impacting the manufacturability.[3]

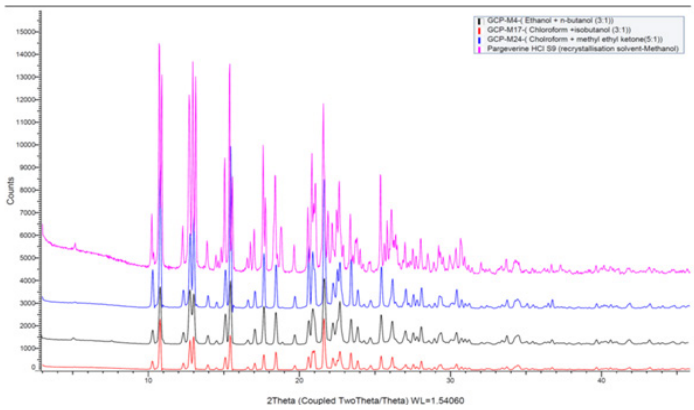

Figure 4: Comparative PXRD pattern of Pargeverine Hydrochloride crystal S9, M4, M17, M24.

Therefore, prior knowledge of the drug's polymorphic forms and the conditions conducive for such transformation is indispensable to place adequate controls at different stages of the chemical reaction or manufacturing process. The experimentation work focused on recrystallization of Pargeverine Hydrochloride in single and mixed solvent systems (50 solvent systems) and evaluating these crystals to determine the formation of polymorph/s. The physical appearance and the melting range of the crystals were not markedly different from the pure drug. The IR spectra of selected crystals could be superimposed on the spectra obtained with the pure drug, indicating similarity in molecular structure. Also, the pattern of heat flow for the phase transition and the peak temperature was similar to the pure Pargeverine Hydrochloride. Selected crystals with code S9, M4, M17, M24 of Pargeverine Hydrochloride were studied for PXRD and all four crystals showed similar diffraction pattern.

This finding implies that the risk of change in physico-chemical properties in Pargeverine Hydrochloride due to polymorph formation during processes like API synthesis and drug product manufacturing involving the listed solvents and mixed solvent systems is very low. Thus, conditions like decrease in drug solubility or bioavailability and in product manufacturability and stability may not arise and hence these processes can be carried out without specific process controls which are otherwise required to arrest polymorph formation.

CONCLUSION

From the study, it can be concluded that there exist minimal possibilities of polymorph formation in Pargeverine Hydrochloride with the selected single and mixed solvent systems.

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CONFLICT OF INTEREST

The authors declare no Conflict of interest.

ABBREVIATIONS

API: Active Pharmaceutical Ingredient; **FTIR:** Fourier Transform Infrared Spectroscopy; **IR:** Infrared; **DSC:** Differential Scanning Calorimetry; **PXRD:** Powder X-Ray Diffraction; **GIT:** Gastrointestinal tract.

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