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Pharmaceutical Applications of Eutectic Mixtures

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A eutectic mixture is defined as a mixture of two or more components which usually do not interact to form a new chemical compound but, which at certain ratios, inhibit the crystallization process of one another resulting in a system having a lower melting point than either of the components [1]. Eutectic mixtures, can be formed between Active Pharmaceutical Ingredients (APIs), between APIs and excipient or between excipient; thereby providing a vast scope for its applications in pharmaceutical industry. Eutectic mixture formation is usually, governed by following factors: (a) the components must be miscible in liquid state and mostly immiscible in solid state [1], (b) Intimate contact between eutectic forming materials is necessary for contact induced melting point depression [2], (c) the components should have chemical groups that can interact to form physical bonds such has intermolecular hydrogen bonding etc., (d) the molecules which are in accordance to modified VantHoff's equation can form eutectic mixtures [3].

Applications of Eutectic Mixtures in Pharmaceutical Industry

During pre formulation stage, compatibility studies between APIs and excipient play a crucial role in excipient selection. Testing for eutectic mixture formation can help in anticipation of probable physical incompatibility between drug and excipient molecules. Eutectic mixtures are commonly used in drug designing and delivery processes for various routes of administration. (Table 1) lists few examples of eutectic mixtures and their application. During manufacturing of pharmaceutical dosage form, it is extremely necessary to anticipate the formation of eutectics and avoid manufacturing problems if any. For example, during tablet compaction the heat produced in the punch and die cavities may lead to fusion or melting of tablet powder compacts leading to manufacturing defects. Thus knowledge of eutectic points of powder components may help avoid these problems. During pharmaceutical analysis, understanding of eutectic mixtures can help in the identification of compounds having similar melting points. Compounds having similar melting points, as a rule will have different eutectic point with a common other component [4]. This knowledge could be used to identify compounds like Ergotamine, Allobarbital etc. (Table 2). The listed drugs can be distinguished by their tendency to form eutectic mixtures with Benzanilide.

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S No	Eutectic Components (a,b)	Ratio	Tm °C (a)	Tm °C (b)	Tm °C (e)	Challenges	Findings
1	Curcumin, Nicotinamide [5]	1:2	181.4	128.3	110.5	Oral route-Low solubility, poor oral bioavailbility	10-fold faster IDR and 6-times higher AUC compared to crystalline curcumin.
2	Ibuprofen, Thymol [1]	2:3	76.0	52.0 [6]	32.0	Transdermal Route-Limited ability to penetrate the skin	A flux of 150 mg/ cm / h, 5.9 times the flux from a saturated aqueous solution with thymol pretreated skin and 12.7 times the flux from a saturated aqueous solution across non-pretreated skin
3	Genistein, PEG 460 [7]	1:24	305.0	2.0	0.2	Parentral Route-Low aqueous solubility, thus formulation difficulty.	Could help in solubilization of geinstein crystals for injection development.
4	Borneol, Menthol (Active 125I-cobrotoxin and eutectic mixture mixed) [8]	1:3	-	-	-	Nasal Route-Blood Brain Barrier	The eutectic mixture of Borneol Menthol, enhanced formulation and passage of active across the blood brain barrier.
5	Menthol and Poloxamer 188, Ibuprofen (Liquid-gel like Suppository) [9]	1:9	-	-	-	Rectal Route-Low bioavailability	Higher AUC as compared to a solid suppository.

Tm: Melting point temperature; E: Eutectic Mixture; IDR: Intrinsic Dissolution Rate; AUC: Area Under Curve; PEG: Poly Ethylene Glycol

Table 1: Applications of eutectic mixtures in formulation development.

S No	Drug	Tm °C	Tm (Eutectic) °C
1	Allobarbital	173.0	144.0
2	Ergotamine	172.0-174.0	135.0
3	Imipramine HCl	172.0-174.0	109.0

Table 2: Eutectic Temperature of Drugs with Benzanilide [4].