CHAPTER 2

Literature Review

As a novel treatment method for superficial lesions, cryospray has experienced global acceptance in the medical fraternity since its inception. Several researchers are working in the following areas to explore its various aspects in order to increase its scope and efficacy in terms of cryoablation:

- Spray characteristics of cryogen
- Influence of equipment modification on cryoablation
- In-vivo experiments in cryotherapy
- Numerical modeling of cryoablation
- Role of adjuvant in cryoablation

2.1 Spray characteristics of cryogen

The amount of cooling produced by cryogen during the spray depends on its interaction with the surrounding. Cryogen sprays are different from liquid sprays in which mechanical forces cause the liquid atomisation. The saturation temperature of cryogens is lower than the ambient conditions, therefore flashing occurs in the cryogen as they interact with the surrounding. Flashing causes primary atomisation of the droplets. Secondary break up occurs due to the surface tension of droplets and velocity difference between the two

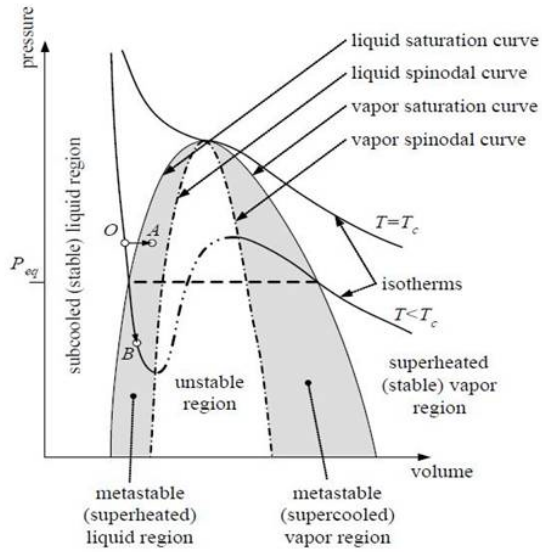

Figure 2.1: Pressure-volume curve for a fluid [20]

phases. Thus, during its (cryogen) flight from nozzle exit to the cooling surface, cryogen exchanges heat and mass with the surrounding.

Flash evaporation in any liquid occurs when the saturated liquid undergoes reduction in pressure below its saturation pressure. There are two ways to initiate flashing in a saturated liquid either by rapid depressurization (process OB of fig. 2.1) or through rapid heating (process OA of fig. 2.1). Rapid depressurization process is generally used for practical applications. It causes liquid to enter into the superheated state. There are four different modes of boiling in superheated state [178]. They are known as (i) homogeneous boiling (ii) wall boiling (iii) particle boiling and (iv) surface boiling. Surface boiling is found to be dominant in flashing jets. During this process, phase change occurs only on the surface of jet whereas the inner core remains in the superheated state. Superheated liquid atomizes through nucleate boiling. Bubble formation and lateral spread of spray depends on the initial stages of nucleate boiling.

Flashing has gained attention of researchers due to its remarkable properties. It aids in increasing the efficiency of various heat transfer and work transfer processes, if carried out in a controlled manner. But, it can be equally catastrophic to mankind if it proceeds in an uncontrolled manner. It is well known fact that latent heat transfer is much more effective than the sensible heat transfer. The prerequisite of swift latent heat transfer is large surface to volume ratio which requires disintegration of liquid sheets. Flashing enables rapid disintegration of liquid sheets into droplet, thus aids in heat transfer due to phase change. Stringent emission norms in case of internal combustion engines, scarcity of water, hazards related with volatile liquid, loss-of-coolent accidents (LOCA) in nuclear power plants, environmental impact of synthetic refrigerants, problems associated with pharmaceutical industries can be dealt effectively once the physics of flash evaporation is understood.

Thus, it can be concluded from above discussions that the applications of flashing are quite diverse from household aerosol cans to rocket engines. The table 2.1 will acknowledge the experimental as well as the numerical studies related to flash evaporation (particularly spray flash evaporation) in order to provide an overview of the studies done so far in this field.

Table 2.1: Studies on flash evaporation

Author	Description	Application
Ahmed [6], 1970	Developed a theoretical model to predict a continuous volumetric vapor fraction profile for both subcooled and bulk boiling regions of a heated channel	Heated channel with inlet subcooling
Darwish et al. [47], 1976	Studied single stage flash evaporation	Desalination technology
Banerjee et al. [13], 1978	Highlighted the need of constitutive relationships for the transfer of mass, energy and momentum at the interface and wall along with the use of conservation equations	-
Reitz and Bracco [135], 1982	Examined the breakup of a high speed liquid jet emanating from a circular nozzle into a stagnant gas environment	Atomisation
Kitamura et al. [90], 1986	Sub atmospheric pressure zone is selected to inject superheated ethanol and water. A correlation between Jakob number and Weber number is proposed	-
Reitz [134], 1987	Effect of liquid inertia, surface tension and aerodynamic forces on jet breakup is studied through multi-dimensional computational model	Atomisation
Lin et al. [100], 1998	Highlighted the work related to breakup regimes	Atomisation

Alatiqi et al. [8], 2004	Studied flash evaporation during desalination process and concluded that flashing rate increases with increase in the system temperature	Desalination technology
Joseph et al. [81], 2005	Studied single stage solar desalination system for solar applications	Desalination technology
Cleary et al. [40], 2007	Used Phase Doppler Anemometer data to develop 1D correlation to predict mean droplet size in the isothermal water jets released in the mechanical breakup regime.	Hazard Analysis
Marsh and O'Mahony [105], 2009	Employed commercial CFD software FLUENT in the development and validation of a three-dimensional numerical flashing flow model for industries	-
El-Zahaby et al. [52], 2010	Investigated the role of stepped solar still in flash evaporation	Desalination technology
Hou et al. [77], 2010	Employed single stage flash evaporation to discuss the effect of nozzle water feed rate, heating air temperature and heating air flow rate	Desalination technology
Kim et al. [88], 2010	Local droplet size of flash swirl spray is measured through Global Sizing Velocitimetry to obtain its spray characteristics	-
Jin et al. [80], 2018	Flash boiling conditions in the superheated fuel spray is estimated through averaged Mie scattering images	High temperature fuel injection
Al-Ghamdi et al. [7], 2018	Visualised the evolution of bubble expansion and burst mechanism in flash boiling jets which is responsible for the jet atomisation	Fuel leaks
Chen et al. [33], 2018	Developed a mathematical model based on the droplet analysis.	Desalination technology
Cai et al. [27], 2018	Proposed a mathematical model based on the diffusion-controlled-evaporation model to acknowledge flash evaporation from a downward jet.	-

Cai et al. [28], 2018	Applied diffusion-controlled-evaporation model to analyse the flashing mechanism in seawater desalination	Desalination technology
Fathinia et al. [55], 2018	Studied flash evaporation system based on low-temperature thermal desalination (LTTD) technology, experimentally.	Desalination Technology
Al-Ghamdi et al. [7], 2018	Recorded flash boiling phenomenon at 5 million frames per second and calculated various parameters like spray angle, velocity, droplet diameter	Fuel leaks
Hao [72], 2020	Bubble growth and rise in a superheated liquid during flash evaporation is studied through mathematical model based on the force balance.	-

"-" diverse application

As far as medical field of cryotherpay is concerned a significant amount of work has been done in the recent past to elucidate the physics behind the flash evaporation (refer table 2.2).

Table 2.2: Applications of flashing in Cryotherapy

Author	Description	Approach / Application	Working Fluid	Result
Kao et al. [82], 2004	Conducted a study on RAFT specimen to optimise the duration of cryogen spray.	Experimental / Cryogen spray cooling	R134a	Cyogenic spurts of 80 ms or less than that are considered favorable in dermatologic laser surgery

Vu et al. [173], 2008	Studied the atomisation and dispersion of flashing sprays. A model is developed to simulate the flashing of a superheated fluid flowing through a medical device. Internal flow characteristics are predicted through a one-dimensional semi-empirical model of refrigerant flow in capillary tube.	Numerical Study/Cryogen spray cooling	R134a	Developed an expression for external vapor/liquid interaction to determine the evolution of droplet size distribution.
Tian et al. [167], 2017	Investigated the role of different cryogens and substrates in the dermatologic cooling	Experimental / Cryogen spray cooling	R134a, R407C, and R404A	Proposed a correlation for maximum heat flux and stated that Weber number is the most important factor in spray cooling. The refrigerant R404A showed the best cooling ability among the refrigerants selected in the study.
Wang et al. [175], 2017	Developed a three dimensional hybrid vortex method to simulate the flashing spray, considering internal flow inside the nozzle. Droplet evaporation and atomisation is also acknowledged	Numerical Study/Cryogen spray cooling	R134a	Predicted the optimum spraying distance on the basis of maximum cooling efficiency

Zhou et al. [191], 2018	Investigated the role of drop dynamics with respect to the operating pressure for R404A refrigerant numerically	Numerical / Cryogen spray cooling	R404A	Concluded that penetration length and droplet velocity reduce with increase in the operating pressure

These studies have established the role of drop dynamics in the successful treatment of lesion through cryospray. The drop dynamics of cryogen depends on various operating parameters like pressure of cryogen tank, nozzle diameter, ambient temperature etcetra. The droplet diameter of cryogen should not be larger than the specified value for a given operating parameter, because larger droplet diameter can cause the splashing of cryogen which is undesirable. However, the droplet diameter below the specified value for a given operating parameter can produce insufficient cooling which is also undesirable. Thus, optimisation of each parameter in cryospray is required before the clinical application.

2.2 Influence of equipment modification on cryoablation

Cryospray is supposed to be a treatment modality suitable for lesions less than 15 mm in diameter. The smaller spray zone of commercial SHN, used in the present scenario, can be attributed as a reason to such constrain. Kumari et al. [97] have shown the role of nozzle diameter and spraying distance on cryoablation. They have used three commercial single hole nozzles of diameter 0.8 mm, 0.6 mm and 0.4 mm in their in-vitro study. Three spraying distances, viz. 9 mm, 18 mm and 27 mm are considered for each nozzle. They further concluded that the spraying distance plays less dominant role in cryoablation than the nozzle diameter. The cryoablation increases with increase in the nozzle diameter. Aguilar et al. [5] have employed flash lamp photography to estimate cryogen spray shape of R134a refrigerant. They developed a novel method to determine the heat transfer coefficient and heat flux at the surface of sprayed object. The refrigerant is sprayed on the aluminum substrate with the epoxy material to consider one dimensional heat transfer model. It has been observed that the nozzle with a larger hole diameter provides almost twice increment in the heat transfer coefficient and heat flux from the substrate than the nozzle with a smaller hole diameter. They further concluded that smaller hole diameter (d = 0.7 mm) produces fine spray as compared to the larger hole diameter (d = 1.4 mm). Moreover, they have also investigated the role of droplet diameter of cryogen spray while varying the nozzle diameters [3]. They advocated that the nozzle length has less influence on the cryogen spray droplet evolution. A comparative study among the four customised and two commercial nozzles is carried by [4] to examine their impact on cooling human skin during laser dermatologic surgery. It has been observed that the heat extraction capacity can be increased while increasing the nozzle diameter and decreasing its length. Tian et al. [167] have introduced the expansion chambers in the straight tube nozzle to enhance the atomisation of cryogen and to lower droplet temperature. They considered five combinations of expansion chambers and concluded that expansion chamber with L:D ratio 1:1 provides the maximum surface heat transfer. A sophisticated approach to control the cooling rate of cryoprobe is applied by Budman et al. [25]. Cooling rate plays an important role in governing the success rate of cryoablation process. They have controlled the cooling rate while controlling the thermal load on the cryoprobe. A heater is wrapped around the cryoprobe to vary the amount of cooling near the probe. Budman et al. [24] further modified the shape of cryoprobes to estimate their influence on the temperature field around them. They considered spherical and cylindrical cryoprobes in their experiments and compared the results with the analytical results. A good agreement between the experimental and analytical results were obtained.

2.3 In-vivo experiments in cryotherapy

In-vitro experiments are frequently conducted to examine the feasibility of innovations in the field of cryosurgery [37, 39, 131, 164, 187]. Especially, experiments conducted on tissue mimicking gel advocate the confirmation of results through in-vivo experiments before going for clinical trials [96, 97, 132]. In-vivo experiments are substantial because they cover each and every aspect of cryotherapy. In-vivo studies in cryospray are few and limited to the case studies only [151, 152, 170] in comparison to cryosurgery where proper experiments are conducted to examine their outcome [59, 144, 181]. The development of effective treatment devices and advancement in imaging techniques [64, 86, 119, 141] can provide cutting edge to cryospray process in the cancer treatment. Therefore, this treatment modality requires to be explored more thoroughly through in-vivo experiments in order to assess the necrotic zone more accurately.

Allington [9] have used the cotton swab and applicator technique in the ablation of cutaneous warts. He considered 154 patients in his study. Zacarian [184] conducted skin temperature measurement with the help of thermocouple at a depth of 2 mm by using copper discs saturated with liquid nitrogen and cotton tipped applicator saturated with liquid nitrogen. They observed that copper disc cylinders are highly effective for malignant and deep-rooted lesions compared to cotton tipped applicator . Breitbart [23] compared the contact and spray method of cryotherapy to quantify the dimensions of ice ball. He also used the moulage to save the healthy tissue from destruction. He further advocated that more cooling can be achieved through spray method than contact method. Because, the ice ball formed with open spray technique is larger than the contact method. A special attention is also paid on predicting the dimension of ice ball with respect to time. It has been observed that ice ball transforms to triangular shape from the semi-circular shape as the time proceeds. A retrospective study comprising of 2932 patients with 4406 new and recurrent basal cell carcinoma and squamous cell carcinomas is conducted by Kuflik [92]. He concluded that cryotherapy provides high cure rate in the treatment of such diseases. Gupta and Kumar [66] have shown successful ablation of keloids through cryotherapy that are irresponsive to intralesional steroids injections. They mounted hypodermic and lumber puncture needles at the tip of the liquid nitrogen dewar cylinders with the help of plastic tube (taken from drip set) and adhesive tape. They considered patients with an age range of 19-50 years whereas the keloids were 1- 12 years old. Two freeze thaw cycles of 20-30 s were given to patients in one session. The patients underwent 5-10 sessions depending upon the size of keloids. Upto 75 % flattening in the keloids were obtained. The cryospray process to treat keloids with an average thickness of 0.2-1.6 cm is also carried out by Barara et al. [15]. The treatment is carried out in six sessions at an interval of 4 weeks. It can be concluded from their study that cryospray provides better results than other therapeutic techniques. Chen et al. [31] highlighted the role of cryotherapy in the treatment of Barrett's esophagus. They used liquid nitrogen and carbon dioxide as the cryogens in their study. They suggested cryotherapy as a treatment of choice for the treatment of dysplastic Barrett's esophagus due to its relatively low cost, ease of use, high efficacy, and low complication rates. Reflectance confocal microscopy is used by Ahlgrimm-Siess et al. [151] to monitor the effect of cryotherapy in superficial Basal Cell Carcinoma. They performed cryotherapy with aged population (mean age 84.5 years) and the tumors were located on the trunk. A 30-year of prospective study in which total, 781 eyelids basal cell carcinoma in 768 patients were examined by Lindgren et al. [101]. They considered cryosurgery as the method of choice for treating this type of BCC. They encouraged cryotherapy due to extremely low recurrence rates and improved aesthetics of the treated eyelids at a low cost compared to other therapeutic modalities. A comparative study of lung cancer ablation with chemotherapy and cryotherapy is carried by Forest et al. [59] after inducing cancer in SCID mouse's lung. The histopathological results suggest that cryotherapy is more efficient in inducing apoptosis than chemotherapy. Researchers have also advocated that chemotherapy and cryotherapy can be used simultaneously in the treatment of such cases in future. Seifert et al. [144] have selected different freeze durations of cryotherapy in their study. Hepatic cryotherapy are performed on 22 pigs followed by laparotomy using a CMS-cryosystem and 8 mm-AccuProbe-Cryoprobes. It has been discovered through thermal results that necrotic zone increases with increase in the freeze thaw cycle. Han [70] highlighted the role of eutectic crystallization during freezing and its influence on direct cell injury. Young et al. [181] conducted an exhaustive in-vitro, ex-vivo and in-vivo study to estimate the isotherms of renal cryotherapy. They used porcine kidney for their in-vivo study and concluded that results of in-vitro and ex-vitro studies are different from the results of in-vivo study.

2.4 Numerical modeling of cryoablation

Apart from in-vivo and in-vitro experiments, numerical studies are also conducted frequently to predict the map of isotherms inside the tissue. Numerical studies are substantial because they eradicate the challenges associated with the experiments. In a numerical approach, differential equations involved in the cryoablation process are solved through finite element, finite difference and finite volume method [57]. Pennes [121] developed the heat transfer model incorporating all the parameters involved in the heat transfer from tissue. He developed the model while conducting experiments on human forearm including the effect of the heat conduction in tissue along with the metabolic heat generation and blood perfusion. The equation formulated by Pennes is termed as Pennes bio-heat transfer equation and it is considered as one of the most important work in the field of bioheat transfer. Comini and Giudice [42] have simulated the freezing of biological system under extreme cold conditions. They have used the finite element method to solve the nonlinear bio-equation. Ramajayam and Kumar [130] proposed a novel approach to reduce the damage to the surrounding healthy tissue caused by cryosurgery while injecting a solution layer of low thermal conductivity around the periphery of tumor. They solved the classic Pennes bio heat transfer equation in their numerical model to simulate the heat transfer in the tissue. Three dimensional phase change process during cryosurgery is simulated by Deng and Liu [48]. They quantified the effect of injection of solution with high thermal conductivity fluid and solution of low latent heat on cryoablation in their study. They further concluded that propagation of ice ball can be controlled effectively through the proposed technique. Peng et al. [120] introduced vasculature as a porous medium in the simulation of coupled bio heat model to analyse the effect of blood perfusion on the heat sink of skin. Finite volume approach is applied by Khademi et al. [84] in the thermal analysis of pulsed cryotherapy. They developed 2D space-time-dependent model while coupling Penne's bio-heat, Navier-Stokes and laplace equation to estimate the thermal profile of the tumor. They also considered the effect of microvascular network in the tumor. Rossi et al. [136] employed bubble packing method to observe the effect of multiple cryoprobes on cryoablation of prostate tumor. Human skin comprises of different layers with distinct property of each layer. Moreover, tumors also possess different property. Therefore, Sarkar et al. [142] presented an analytical solution of Penne's bio-heat transfer equation for multilayer skin model. They also included the effect of metabolic heat generation and blood perfusion in their numerical model. Apart from these, table. 2.3 acknowledges the notable studies regarding the effectiveness of cryoprobes in cryosurgery.

Table 2.3: Numerical studies on cryoablation

Author	Description	Result
Bischof et al. [19]	Applied finite difference technique to analyse the freezing process of lung tissue through cryosurgery	They have observed three distinct characteristics of convective freezing of lung tumor.
Hoffman and Bischof [75]	Developed a two dimensional transient axisymmetric model to predict freezing and thawing behavior in dorsal skin flap chamber	Obtained a numerical solution with enthalpy method while incorporating heating due to blood flow. They have concluded that the model more closely approximates the freezing process than the thawing process.
Etheridge et al.[54]	The finite element approach is used to model heat transfer from cryoprobe while applying convective boundary condition on the probe tip	They have concluded that the more accurate prediction of thermal history can be obtained through convective boundary condition than constant heat flux and constant temperature boundary conditions.

Rabin and Shitzer [129]	Considered tissue as a non ideal material where phase transition occurs over a temperature range and presented a combined solution of inverse Stefan problem. Included the thermal effects of metabolic heat generation and blood perfusion in the tissue	It has been concluded that blood perfusion does not produce significant effect on the freezing front location. However it does affect in thawing stage significantally.
Zhang et al. [185]	Designed a computational domain based on the MRI imaging of real prostate tumor.	Suggested that the thermal profile of the tumor during cryosurgery should be predicted through numerical simulations before proceeding for the clinical surgery.
Nakayama at al. [115]	Experimentally and numerically traced the freezing front of the tumor during cryosurgery	Obtained a limiting radius of tumor that can be treated through a single cryoprobe. Time required to kill entire tumor is also quantified in the study.
Beckerman et al.[17]	They have shown the influence of thermally significant blood vessel on cryotherapy	They have considered surface cryoprobe for their study. The heat sink of tissue depends on the flow in the blood vessel.
Chua [36]	Developed a numerical model to study cryotherapy in unresectable liver tumors	The study mainly focus on large tumors. It has been observed that multiprobe method with 3 cryoprobe can treat tumors with higher degree of irregularity
Chua and Chou [37]	Studied the impact of multiple freeze thaw cycle on cryoablation	Concluded that the multiple freeze thaw cycle increase the volume of cryoablation

Kumar [93]	Developed a three dimensional numerical model to highlight the role of central probe cryosurgery	Two arrangements of multiple cryoprobe is compared; (i) four offset cryoprobes with central probe and (ii) four offset cryoprobe without central probe. It has been observed that the necrosis has increased by 57 % with marginal increase in cooling power with four offset probe with central probe arrangement than four offset probe without central probe arrangement.

A few notable numerical studies are also available in the field of cryospray. Sun et al. [160] obtained the thermal history of skin for 30 s of freezing through their numerical model. They considered different values of heat transfer coefficient (104 W/m^{2}K, 105 W/m^{2}K, and 106 W/m^{2}K) within 5 mm spray zone to predict the thermal profile in a multilayer skin model. The convective heat transfer coefficient is assumed to be 50 W/m^{2}K in region other than spray zone whereas it is assumed to be 10 W/m^{2}K for thawing duration. Researchers [159] have also quantified the mechanism of ice formation and the dimension of intracellular and extracellular ice formation in the tissue through their numerical model. Mercer et al. [110] proposed a new approach to save healthy tissue from cryospray. They encouraged the application of low thermal conductivity gels like glycerin around the periphery of lesion to protect them from cryoablation. Kumari et al. [96–98] applied a time dependent temperature boundary condition on the spray zone to simulate the freezing process in the tissue . They have estimated the boundary condition of spray zone on the basis of experimental readings of thermocouple.

2.5 Role of adjuvant in cryoablation

Surgeons are always concerned about the recurrence and metastasis of skin cancer. Rowe et al. [137] highlighted the risk factors associated with recurrence and metastasis of squamous cell carcinomas. It has been revealed that one of the characteristics of high risk lesions is diameter larger than 2 cm and depth greater than 4mm. The current method of cryospray is suitable for lesions less than 15 mm in diameter [170]. Moreover, similar problem exists in the cryosurgery as well. Because, during the treatment of larger lesions, cell destruction does not take place effectively at the edges of the tumor. Adjuvants are used in both the fields to enhance the cell destruction at the edges of tumor. Researchers have paid special attention to enhance the understanding of phase change process in the presence of various concentrations of NaCl in cryobiological media [50, 71]. Intracellular ice formation through eutectic crystallization is found to be major mechanism of cell destruction when different saline solutions (NaCl, KCl, KNO_3) are used to analyze the freezing conditions in rat's prostate tumor [70]. The same group has conducted a detailed study to understand the freezing effect of salt solution in the tissue through differential scanning calorimeter, cell viability and cryomicroscopy. They have concluded that the presence of salt solution in tissue or cell reduces the freezing point and increases the necrotic zone [68, 69]. Glycine as adjuvant is also explored by Wang et al. [174] to minimise the incomplete cryodestruction on the edges of MCF-7 human breast cancer cell at mild freezing/thawing conditions via eutectic solidification. Goel et al. [63] reviewed the impact of various adjuvants like thermophysical agents, chemotherapeutic, vascular agents and immunomodulators in cryotherapy. They have concluded that each adjuvant has significant impact on the outcomes of cryosurgery, but more investigation is needed before proceeding for clinical trials. As far as preservation of tissue bowl surrounding lesion is concerned, injection of low thermal conductivity fluid around the lesion and its impact on cryotherapy can be analysed through the work of Ramajayam et al. [130]. They mentioned that the fluid layer affects the rate of heat transfer and also serves as an insulating layer between the healthy and unhealthy tissues.

The biocompatible nanoparticles are also extensively used in the cryosurgery process [48, 63, 78, 84, 182]. This process is specifically suited to inner organs. A solution loaded with nanoparticles is injected inside the tissue and enhancement in necrosis is achieved through extreme cooling. Administration of nanoparticles improves the thermal conductivity of the tissue and increases the rate of tissue destruction. Zhang et al. [187] suggested that administration of Fe_3O_4 nanoparticles inside the tissue can increase the rate of freezing leading to faster cell destruction. A study conducted on healthy male rabbit by Di et al. [51] to examine the role of MgO nanoparticles in cryosurgery revealed that nanoparticles promote and enhance the cryoinjury. Proper selection and dosing of nanoparticles are very important parameters in such studies, as they are administered in the living organisms. Yan and Liu [180] studied the impact of Fe_3O_4, diamond, carbon nanotubes and silver nanoparticles in cryosurgery through their computational model. They further reported that choosing optimal concentration with appropriate particle plays an important role in maximising the cryoablation. Singh and Bhargava [153] developed a numerical model with element free Galerkin method to simulate the behavior of Al_2O_3, Fe_3O_4 and gold nanoparticles in cryosurgery. They also studied the effect of particle size and concentration of nanoparticles on freezing process and concluded that gold nanoparticles are providing maximum freezing efficiency.

It can be concluded from the aforementioned discussion that a significant amount of work has been done in the area of cryosugery using adjuvants, but the area of cryospray is less explored by the researchers. The challenges associated with the transdermal transport of adjuvant through stratum corneum is the reason for the rare application of adjuvant administration techniques in the field of cryospray [126]. However, recent advancements in third generation transdermal delivery systems like microneedles, thermal ablation, microdermabrasion, electroporation and cavitational ultrasound [16, 125, 127] have improved the transdermal transport. Successful administration of drugs through transdermal route has also been reported [53, 104, 163, 188]. This has opened a new window for cryospray based treatment of cancerous lesions through adjuvant administration. The advantages of transdermal delivery are: variable rate of delivery of drugs, its ease of use, and economic feasibility as compared with the other therapies (eg. oral or intravenous administration) [145]. The innovations in the field of nanotechnology has provided leverage to researchers in the synthesis of nanometersized drugs for various biomedical applications [116]. Nanoparticles assisted drug delivery has gained immense popularity in dermatology such as photoprotection, barrier creams, and the treatments of hair disorders. Kumari et al. [96] suggested NaCl as an adjuvant in the treatment of skin cancer through cutaneous cryospray. They concluded that the ablation volume in phantom increases with the increase in the concentration of adjuvant. The end temperature and ice front are found to decrease substantially with increase in the concentration of adjuvant in the phantom.