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Development Of Rapidly Dissolving Oral Thin Film With Dexamethasone: Exploring An Approach For Managing Nausea In Cancer Chemotherapy

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***Abstract*:-** Cancer patients still struggle greatly to control the nausea and vomiting brought on by treatment. Tetrahydrocannabinol and metoclopramide hydrochloride are two less effective traditional antiemetics than phenothiazines. Our findings and those of many pilot trials suggest that high glucocorticoid dosages help reduce the nausea and vomiting that come with cancer therapy. Still, some cancer patients suffer negative side effects from their drugs; the most frequent ones are nausea and numbness. Chemotherapy-induced nausea and vomiting (CINV) may occur gradually or suddenly. After starting chemotherapy, acute emesis manifests 24 hours later; delayed episodes follow and may last over several days. It is recommended to use dexamethasone, aprepitant, a 5-HT3 receptor antagonist, or both as a pretreatment to prevent acute emesis. For delayed emesis caused by moderately to highly emetogenic anticancer medicines, oral dexamethasone, either by itself or in combination with aprepitant, is advised. Oral mucositis makes administering oral antiemetic medications more difficult. It is the cause of dysphagia and other swallowing difficulties in patients with head and neck cancer undergoing radiation and chemotherapy. To aid patients who have difficulty swallowing, jelly formulations and oral dissolving tablets have been developed. Although the insoluble portions of oral disintegrating tablets remain in the mouth until they are taken, they disintegrate quickly and may be a bit uncomfortable to take. Though often hefty, these formulations are helpful for elderly people who have trouble swallowing. Furthermore, dental care products have made use of edible thin oral film formulations that dissolve readily in saliva without the need for water. Particularly helpful are these oral disintegrating thin film formulations for those who have trouble swallowing and eating.

Keywords:- Dexamethasone, Emesis, Chemotherapy-induced nausea vomiting, Oral thin film

I. Introduction

Most cancer patients have various side effects from their therapies, which may significantly impair their quality of life and make managing these issues challenging for both the patient and their doctors(1). Chemotherapy-induced nausea and vomiting (CINV) is one of the most common and troublesome side effects(2). Patients may find it difficult to follow their treatment regimens as a result of these symptoms; some may decide to forego treatment entirely or postpone chemotherapy cycles out of concern about contracting CINV(3). Cancer patients and their caregivers remain extremely concerned about managing acute chemotherapy-induced vomiting (CIV), chemotherapy-induced nausea (CIN), anticipatory nausea and vomiting (ANV), and delayed nausea and vomiting (DNV), despite significant advancements in this field(4).

The oral route is one of the most practical, economical, and favoured methods of medication administration among all the drug delivery routes(5). However, certain patients, particularly those who are younger or older, have trouble chewing or swallowing certain oral solid dose forms, such as hard gelatin capsules and tablets(6). They cannot take these dose types because they are afraid they may suffocate. Several fast-dissolving drug delivery systems (FDDDS) were developed as a solution to this problem(7). One way to avoid problems such increased first-pass metabolism and drug degradation in the gastrointestinal system is to provide medicine buccal(8). The development of several dose forms, such as wafers, modified-release tablets or capsules, traditional tablets, orally disintegrating tablets, and, most recently, fast-dissolving oral thin films, has been made possible by advancements in oral drug delivery technology(9). Ultrathin, fast-dissolving oral thin films are used on the tongue or buccal cavity; they are made of a hydrophilic polymer that hydrates or adheres rapidly(10). Without the need for water or chewing, these films melt or disintegrate in a matter of seconds to release the active component(11). Due to the mucosa's abundant blood supply, first-pass metabolism is avoided, resulting in rapid medication absorption and bioavailability(12). Because of this, oral thin-film technology is perfect for medications with high first-pass metabolism, since it may improve patient compliance and bioavailability. This technology is still in its infancy but has great potential(13).

II. Pathophysiology

- **General Pathophysiology**(14)

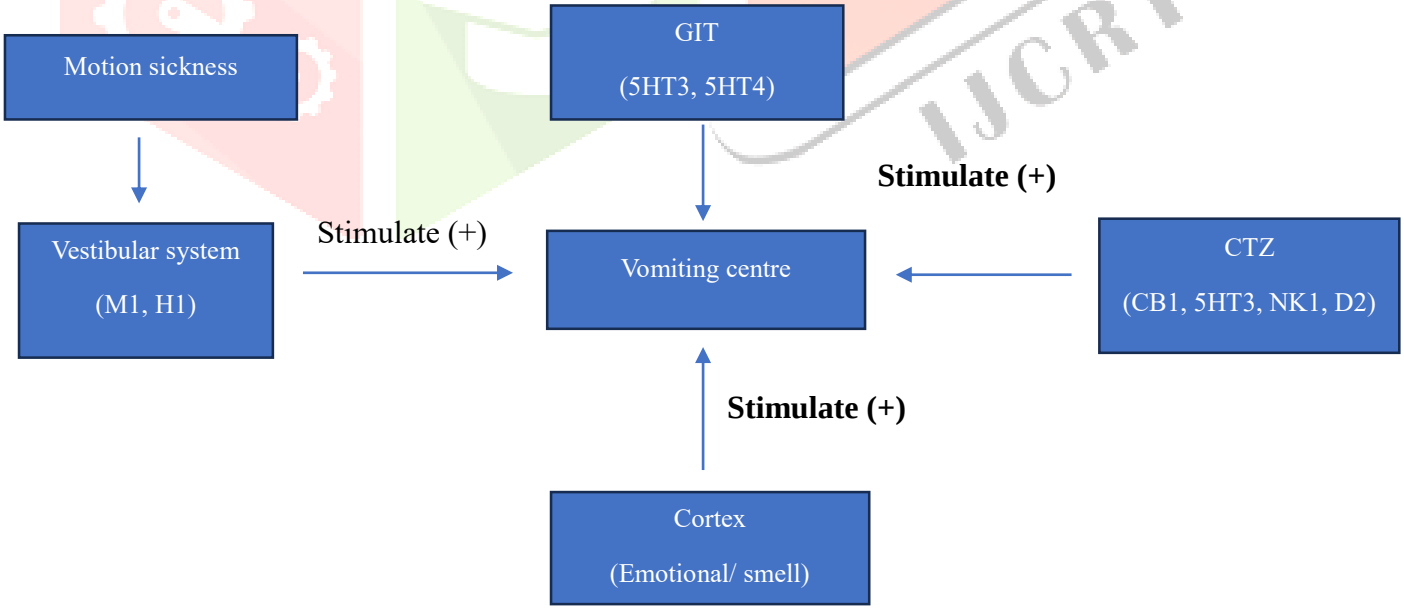

Figure 1 Pathophysiology of emesis

The vomiting reflex starts when the vomiting center in the medulla becomes activated. The emetic response is initiated when this center gets signals from both central and peripheral channels(15). The peripheral pathway starts in the gastrointestinal system, where abdominal vagal afferents provide signals like pharyngeal discomfort and stomach or duodenal distension(16). On vagal afferent fibers are several receptors, including 5-HT3, neurokinin (NK) 1, and cholecystokinin-1. These receptors may become active, and 5-HT3 is the primary mediator of the emetic reflex(17). Where these fibres terminate is in the dorsal vagal complex, which

also contains the nucleus tractus solitarius (NTS), the area postrema, and the dorsal motor nucleus. The NTS and, to a lesser extent, the postrema area known as the "chemoreceptor trigger zone," send this information to the vomiting center(18).

However, an emetic response is brought on by the central emesis pathway, which is activated by brain impulses and activates the vomiting area(19). Vomiting may result from the sudden release of cholinergic and histamine neurotransmitters into the ventral canal (VC) in reaction to pain, aberrant vestibular function, or emotional stimuli(20). Moreover, the ventricle receives signals from the chemoreceptor trigger zone, which is situated in the postrema region of the fourth ventricle, in response to chemical stimuli like chemotherapy and endogenous toxins(21). The neurotransmitter serotonin (5-HT) and its receptors, the D2 and D3 dopamine receptors in the postrema region, the dorsal motor nucleus, NTS, substance P, and the NK1 receptor are all part of this system(22).

III. Chemotherapy and the emetic response

Chemotherapeutic agents may stimulate neurotransmitter receptors in the brain's postrema zone (CTZ) or vagal afferents close to the intestine's enterochromaffin cells(23). The oxidative activity of free radicals produced by chemotherapeutic medicines activates the peripheral route 24 hours after chemotherapy starts, causing the enterochromaffin cells in the stomach to release serotonin(24). Subsequently, serotonin triggers the peripheral vomiting route by activating abdominal sensory vagal fibres, which in turn triggers the emetic response via the VC. Therefore, peripheral pathway activation is the etiology of acute CINV(25).

Drugs used in chemotherapy may release substance P into the central and peripheral neural systems, therefore causing vomiting mediated by NK1(26). The overwhelming amount of data suggests that nausea brought on by substance P release resulting from chemotherapy is caused by centrally expressed NK1 receptors, notably those present in the NTS and region postrema(27). The hypothesis that delayed CINV is mostly caused by central NK1 activation is supported by the findings of therapeutic trials with 5HT3 and NK1 receptor antagonists(28). Notably, nausea and vomiting in cancer patients can be caused by radiation therapy, drugs taken outside of chemotherapy, metabolic effects associated to cancer, gastrointestinal obstruction, difficulty emptying the stomach, metastases to the brain or spinal cord, and other factors like pain or anxiety(29).

IV. Dexamethasone as anti-emetic

Prednisolone and methylprednisolone are two more synthetic glucocorticoids that share dexamethasone's anti-inflammatory and anti-allergic characteristics(30). More than 30 years ago, it was discovered that dexamethasone might effectively stop chemotherapy-induced nausea and vomiting (CINV). Dexamethasone and similar glucocorticoids may lessen radiation-induced nausea and vomiting (RINV), according to further study. According to the MASC degree of confidence study, dexamethasone reduces both acute and delayed CINV moderately to extremely effectively(31). This effectiveness is also shown by two other widely used types of antiemetics: tachykinin NK1 receptor antagonists (like aprepitant) and 5-hydroxytryptamine 3 (5-HT3) receptor antagonists (like ondansetron)(32).

V. Mechanism of action of Dexamethasone

5.1 Antiemetic action related to anti-inflammation

After irradiation, the local tissue showed an increase in the number of inflammatory mediators. Radiation-exposed guinea pigs had higher amounts of prostaglandins and thromboxane B2 in their pulmonary airways(33). Similarly, during the eighteen-day post-irradiation period, prostaglandin levels were greater in the liver and brain of irradiated rats. Furthermore, several anti-inflammatory drugs (including ibuprofen, indomethacin, and meloxicam, which are cyclooxygenase inhibitors) considerably reduced the emesis caused by cytotoxic drugs and radiation. In cancer patients, ibuprofen effectively reduced radiation-induced neutrophil leakage(34). In dogs receiving radiation therapy, indomethacin significantly reduced emesis. Indomethacin and meloxicam both reduced the emesis that cisplatin caused in pigs. These results imply that chemotherapy- and radiation-induced nausea and vomiting (CINV and RINV) may be related to the inflammatory process(35).

Depending on the drugs used, their doses, and the precise areas and places that radiation is directed at, both chemotherapy and radiation therapy have the potential to kill tissue to differing degrees(36). An increase in the synthesis of inflammatory mediators such as eicosanoids may result from this injury. Membrane lipids are the source of eicosanoids, which include hepoxilins, prostacyclins, prostaglandins, thromboxanes, leukotrienes, and lipoxins(37). Numerous physiological, pharmacological, and hormonal variables affect the activation of acyl hydrolases, which produce arachidonate. Anti-inflammatory medications, such as glucocorticoids and cyclooxygenase inhibitors, might decrease eicosanoids' synthesis and perhaps enhance their antiemetic effects in patients receiving chemotherapy and radiation treatment(38).

5.2 Antiemetic action related to serotonin

A number of neurotransmitters, including 5-HT, have been shown to cause vomiting . Glucocorticoids impede the synthesis of 5HT(39). In experiments with peripheral blood mononuclear cells, methylprednisolone reduced the release of 5-HT induced by cisplatin. Both methylprednisolone and dexamethasone reduced the expression of 5-HT3A receptors in Xenopus laevis oocytes in a concentration-dependent manner(40). Dextamethasone decreased the levels of 5-HT in the hippocampus and cerebral cortex of developing rats. Mice with central glucocorticoid receptor ablation showed an increase in 5-HT2A receptor expression and function. The antiemetic effects of glucocorticoids may be explained by these mechanisms(41).

VI. Materials and methods

6.1 Materials(42)

Dexamethasone and ethyl-p-hydroxybenzoate, Microcrystalline cellulose, Polyethylene glycol, Polysorbate 80, 5% low-substituted hydroxypropyl cellulose and hydroxypropyl methylcellulose, are used as film base.

Table 1 Materials required for formulation

Component	Ingredients
Drug	Dexamethasone
Film forming material	Microcrystalline cellulose, 5% low-substituted hydroxypropyl cellulose and hydroxypropyl methylcellulose
Solvent	Polyethylene glycol, Polysorbate 80

6.2 Methods

- Solvent casting method
- Rolling method
- Hot melt extrusion method
- Solid dispersion method

6.2.1 Solvent casting method(43)

A popular technique for creating oral thin films (OTFs) is solvent casting, which provides exact control over the consistency and thickness of the film(44). This method creates a homogenous solution by dissolving a polymer matrix in an appropriate solvent. To get the intended therapeutic effect and film characteristics, the solution may additionally include additional excipients and active pharmaceutical ingredients (APIs)(45). In order to create a thin film, the solution is then poured onto a level surface, such a glass plate or stainless steel sheet, and let to dry or evaporate under carefully monitored circumstances. A solid film with the required drug content and mechanical qualities is formed when the solvent evaporates. Cutting the film into the proper sizes and packaging it for oral delivery are possible next stages(46). Several benefits come with solvent casting,

including as formulation diversity, scalability, and the possibility to insert heat-labile or sensitive medicines into the film matrix. To guarantee the final product's purity, stability, and biocompatibility for safe oral distribution, however, rigorous solvent selection and processing parameter optimization are crucial(47).

The water-soluble polymers and plasticizers are combined with a suitably volatile solvent, such as distilled water or ethanol, to create a transparent, viscous mixture.

In the magnetic stirrer, the solution is agitated for two hours and then set aside.

Aqueous solvent is used to dissolve API and other components, which are then mixed with the main drug.

Through vacuuming, the trapped air is released.

Lastly, the solution is cast onto a suitable Petri dish and baked for 24 hours at 50 degrees Celsius.

The film is cut to the appropriate dimensions.

Water-soluble polymers and plasticizers are mixed with an appropriately volatile solvent (distilled water or ethanol) to form a clear, viscous slurry. After two hours of vigorous stirring with a magnetic stirrer to guarantee complete mixing, this solution is put away. The active pharmaceutical ingredient (API) and other required ingredients are dissolved in an aqueous solvent in a separate stage. After then, the primary medication is mixed with this combination. The solution is vacuumed to remove any air that may have been trapped. After that, the mixture is transferred to an appropriate Petri dish and baked for 24 hours at 50 degrees Celsius to create a firm film. After the film is baked, it is cut to the proper size for the purpose for which it is intended.

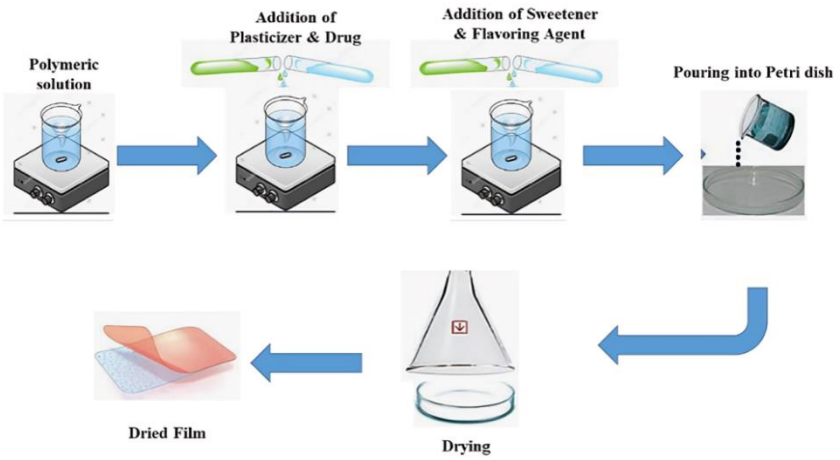

Figure 2 Solvent casting method*(43)*

6.2.2 Rolling method(43)

In several sectors, including flexible electronics and semiconductor fabrication, the rolling method is a commonly used technique for the creation of thin films(48). Using a sequence of rollers and regulated pressure and temperature, a substrate material—typically a metal or polymer—is fed through this process. First, the precursor material—which might be a molten polymer, a solution, or a suspension—and the substrate are fed into the rollers. The precursor material forms a thin coating on the substrate's surface as it passes through the rollers in an even manner(49). Large-scale manufacturing is possible because to the substrate's continuous motion and the rolling action, which guarantees precisely regulated film thickness. This process is also popular for a variety of industrial applications because to its benefits, which include high throughput, scalability, and the capacity to create films with customized qualities(50).

First, a pre-mix is made using polar solvent, film-forming polymers, and other additives—medication is not included.

↓

Add the necessary quantity of medication to the pre-mix.

↓

To create a homogeneous matrix, the medication and pre-mix are combined.

↓

The resultant mixture is introduced into the roller.

↓

The film is formed and carried away by a support roller

↓

Controlled bottom drying is then used to dry the wet film.

↓

The film is cut to the appropriate dimensions.

Prior to adding the drug, a pre-mix is made using polar solvent, film-forming polymers, and other ingredients. The pre-mix is then supplemented with the required amount of medicine. The drug and pre-mix are completely mixed to form a homogenous matrix. The resulting mixture is then fed into the roller, which forms the film and removes it with the help of a support roller(31). The moist film is then dried by regulated bottom drying. The dried film is then finally trimmed to the proper size for the purpose for which it is intended.

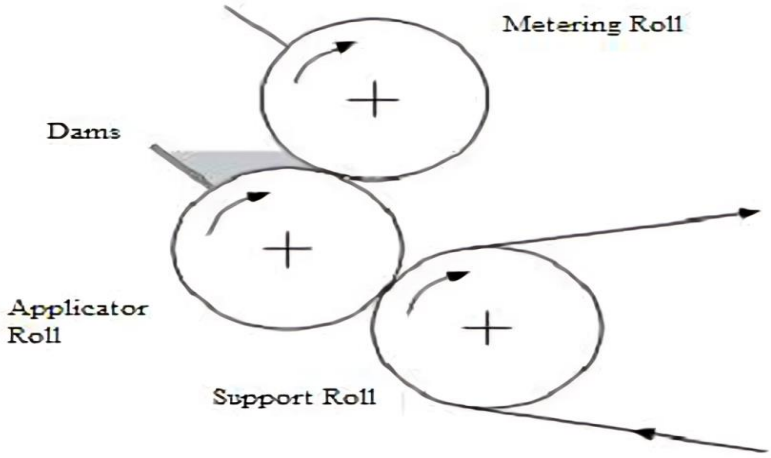

Figure 3 Rolling method*(43)*

6.2.3 Hot melt extrusion method(43)

In the production of pharmaceuticals, hot melt extrusion (HME) is a flexible method often used to create solid dispersions that improve the solubility and bioavailability of poorly water-soluble medications(51). With this process, a drug-polymer combination is blended and extruded through a heated barrel and die using mechanical forces and heat. The outcome is a homogenous molten mass that cools and solidifies. The process's continuous nature, lack of solvents, and capacity to create several dose forms such granules, pellets, and films make it useful(52). Moreover, HME makes it possible to combine many excipients and active components, which simplifies the creation of intricate drug delivery systems with regulated release profiles. The technique is essential to contemporary pharmaceutical research and development because of its well-documented potential to improve drug dissolving rates and stability(53).

Granules, sustained release tablets, transdermal, and transmucosal drug delivery methods are often prepared using it.

At first, the medication is combined with solid carriers.

Melt the mixture using a heater-equipped extruder.

Ultimately, the dies form the melt into films.

This procedure is often used to make granules, sustained release pills, transdermal, and transmucosal drug delivery techniques. The medicine is first mixed with solid carriers(54). An extruder fitted with a heater is then used to melt this mixture. The dies finally shape the melted liquid into films so that it may be treated further for the desired drug delivery strategy.

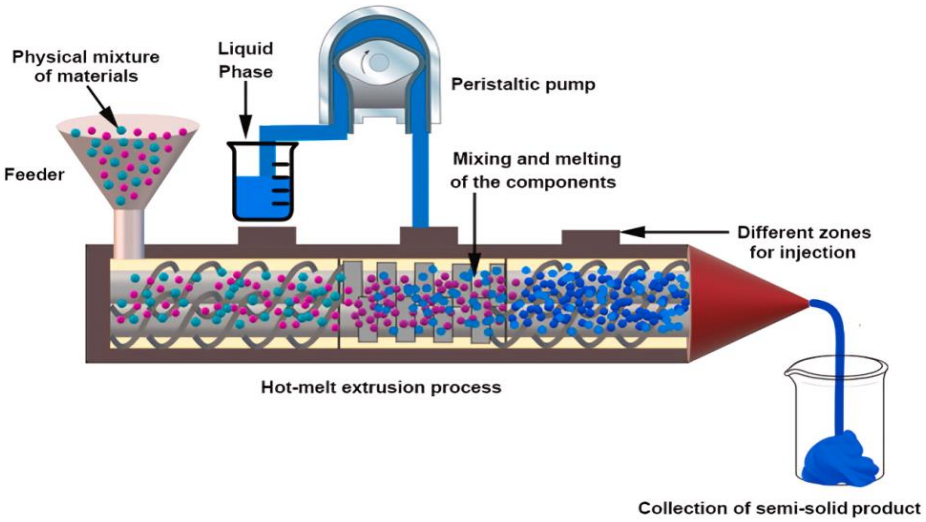

Figure 4 Hot melt extrusion*(43)*

6.2.4 Solid dispersion method(43)

A frequently used approach for creating oral thin films (OTFs) is the solid dispersion method, which improves the solubility and bioavailability of medications that are not very water soluble(55). Using techniques like melting, solvent evaporation, or spray drying, the active pharmaceutical ingredient (API) is evenly distributed inside a hydrophilic polymer matrix in this procedure. The resultant solid dispersion is then mixed into the thin film formulation, which is then dried and cast to create a thin, flexible film that may be taken orally(56). This method improves absorption and therapeutic effectiveness by helping the medication dissolve in the gastrointestinal system. Solid dispersion-based OTFs are attractive options for the delivery of a variety of pharmaceutical substances because they have benefits such improved drug stability, dosage precision, and simplicity of administration(57).

This approach involves dispersing one or more active substances in an inert carrier in a solid form, with the presence of amorphous hydrophilic polymers(58).

To create a solution, API is dissolved in an appropriate solvent.

Without draining the liquid solvent, solution is added to the melt of a suitable polymer (PEG) below 70 oC.

Ultimately, solid dispersions are formed into films using dies.

One or more active compounds are firmly distributed in an inert carrier by use of amorphous hydrophilic polymers. The active pharmaceutical ingredient (API) must be first dissolved in the appropriate solvent in order to form a solution. This solution is then applied, without draining the liquid solvent, to a melt of a suitable polymer, such as polyethylene glycol (PEG), maintained below 70°C. Solid dispersions are finally produced by dies into films, which allow further processing as needed.

7 Evaluation parameters

7.1.1 Dosage uniformity(42)

Using 20 preparations, the oral film preparation's dose homogeneity was verified, and spectrometric determination of the dexamethasone content was achieved by HPLC. As per the JP15, the preparation's acceptance value (AV) is below 15%. The following formula is used to get the AV for JP15:

$$AV = |M-X| + ks,$$

where s is the standard deviation, k is the acceptability constant (2.2), X is the average (%) of individual contents, and M is the label claim (100%). In USP27, the relative standard deviation must be less than or equal to 6.0% and the primary component's contents must fall between 85% and 115% of the range.

7.1.2 **Stability test**(42)

The amount of dexamethasone in a piece of film preparation is measured after it has been kept for four to twenty-four weeks in an aluminium container at 25 degrees Celsius and 50 to 60 per cent humidity (regular conditions) or 40 degrees Celsius and 75 per cent humidity (accelerated conditions). Additionally, a dissolving test is performed on the film sample.

7.1.3 **Dissolution test**(42)

We use the JP15 paddle method and the paddle equipment to carry out the dissolving test. We spin 900 mL of pH 1.2 phosphate solution at 50 rpm as the test solution at 37 ± 0.5 C(59). Every two to sixty minutes, an autosampler was used to collect ten milliliter aliquots of material, to which the same amount of new test solution was added(60). An HPLC was used to measure the concentration of dexamethasone after a 50-liter aliquot of the mixture was added to a one milliliter aliquot of the samples in a polyethene tube along with the same amount of the internal standard solution (4 mcg/mL)(61).

7.1.4 **Thickness test**(42)

The film's thickness indicates the drug's precise dosage. The micrometre screw gauge or calibrated digital Vernier callipers are used to measure it at five distinct critical places. The resultant mean value is computed to determine the final film thickness. The ideal range for the film's thickness is between 5 and 200 μm.

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