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Formulation of Rapid Dissolving Films Containing Granisetron Hydrochloride and Ondansetron Hydrochloride

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ABSTRACT

The oral mucosa is conveniently and easily accessible and therefore allows uncomplicated application of dosage forms. A rapid-dissolving drug delivery system, in most cases, is a tablet that dissolves or disintegrates in the oral cavity without the need for water or chewing. More recently, fast-dissolving films are gaining interest as an alternative to fast-dissolving tablets to definitely eliminate patients' fear of chocking and overcome patent impediments. In the present study, calculations for amount of drugs were determined, Rapid dissolving films containing GSH were prepared using solvent casting method. An aqueous solution of polymer was prepared in distilled water. For preparing the solution, polymer was soaked in water for some time (wherever required). This was followed by addition of GSH in the aqueous solution of the polymer. Now, plasticizer (PEG 400 and/or Glycerol), sweetening agent (Aspartame and/or Sucralose), citric acid and flavor were also added to this solution. In-vitro disintegration time (DT) of the prepared rapid dissolving films was determined visually in a glass beaker containing 50 ml water and swirling every 10 seconds. Average of 3 films was taken for this purpose. *In-vivo* DT of the prepared rapid dissolving film was determined by mouth in three human volunteers. Evaluation of taste was done by a taste panel with 2mg drug and subsequently one film held in the mouth for 10-15 seconds. For preparing rapid dissolving films, varying amount of Pullulan, METHO K3P, METHO E3P were taken. Solvent evaporation method was used for preparation of the film. Various polymers used in the study were: Pullulan, Metho K3P, Metho E3P, Metho E15P and Poly N10. PEG-400 and glycerol were used as plasticizer. Aspartame and sucralose were used as sweetening agent while citric acid was used as saliva stimulating agent

Keywords: Rapid dissolving film, Ondansetron hydrochloride (OND), Granisetron Hydrochloride (GSH).

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1. INTRODUCTION:

The oral cavity has been investigated as a site for drug delivery for a long period of time. In 1847 Sobrero found that nitroglycerine was absorbed from the oral cavity. Since then various active substances have been investigated for local or systemic use. Drug delivery through the oral cavity offers many advantages. The oral mucosa is conveniently and easily accessible and therefore allows uncomplicated application of dosage forms. Furthermore, the oral mucosa is robust against local stress or damage and shows fast cellular recovery after such incidents. Active Substances can be administered locally to treat oral diseases like periodontal disease, bacterial and fungal infections or aphthous stomatitis. A systemic action can be achieved via drug permeation through the mucosal endothelium. For systemic drug absorption, various dosage forms and devices, e.g. buccal patches, buccoadhesive discs and mechatronic delivery devices have recently been developed. The use of buccal patches allows drug absorption to be terminated immediately upon simple removal of the patch. The aforementioned advantages of drug administration via the oral cavity offer new possibilities in the administration of drugs to "problematical" subpopulations like children and the elderly. These patients have special drug administration requirements as they are often unable to swallow solid dosage forms (e.g. tablets, capsules).

A rapid-dissolving drug delivery system, in most cases, is a tablet that dissolves or disintegrates in the oral cavity without the need for water or chewing. Most rapid-dissolving delivery system films must include substances to mask the taste of the active ingredient. This masked active

ingredient is then swallowed by the patient's saliva along with the soluble and insoluble excipients.

1.1 Research & Development of the Technology:

One of the primary objectives in developing the rapid dissolving drug delivery system was to identify and satisfy an unmet need of general and specific populations (pediatric and geriatric patients) and to improve compliance and dosing ease for the patient. This system is a fast-dissolving film that allows children, elderly, and the general population to take their medications discretely wherever and whenever needed, satisfying an unmet need. Table below summarizes the special features and advantages of a film drug delivery system.

Table 1: Special features and advantages of a film drug delivery system

Special features	Advantages
Thin elegant film	Convenient dosing
Various sizes and shapes	No water needed
Unobstructive	No risk of choking
Mucoadhesion	Taste masking
Fast disintegration	Enhanced stability
Quick dissolving	Improved patient compliance
Rapid release	Life cycle management

Fast Dissolving Tablet (FDT): Recently fast dissolving drug delivery systems have started gaining popularity and acceptance as new drug delivery system, because they are easy to administer and lead to better patient compliance. They also impart unique product differentiation thus enabling use as line extension for existing commercial products. FDTs can be prepared by various techniques like direct compression, sublimation, melt granulation, moulding, volatilization and freeze drying.

1.2 Rapid Dissolving Films (RDFs):

More recently, fast-dissolving films are gaining interest as an alternative to fast-dissolving tablets to definitely eliminate patients' fear of chocking and overcome patent impediments. Fast-dissolving films are generally constituted of plasticized hydrocolloids or blends made of thereof that can be laminated by solvent casting or hot-melt extrusion. Thin film drug delivery, also referred to as orally dissolving thin film, and has emerged as an advanced alternative to the traditional tablets, capsules and liquids often associated with prescription and OTC medications. Similar in size, shape and thickness to a postage stamp, thin film strips are typically designed for oral administration, with the person placing the strip on or under the tongue or along the inside of the cheek.

2. EXPERIMENTAL WORK/ FORMULATION STUDIES

2.1 Calculation for amount of drug

Diameter of Petri Dish = 9.6 cm,

So area of petri dish = 72.4 cm^2

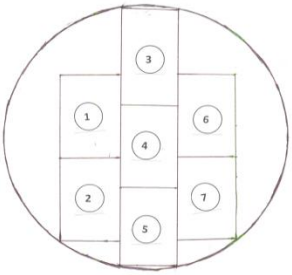
Size of film: 3x2 cm^2 (= 6 cm^2),

So required amount of GSH in one petri dish will be equivalent to 12 film (=72.4 cm^2/6 cm^2).

Dose of GSH per strip = 2.24 mg (equivalent to 2 mg Granisetron base),

So amount of GSH taken per petri dish = 2.24x12 = 26.88 mg (27 mg)

Actual/final number of film obtained from each petri dish (after cutting into size of 3x2 cm^2) = 07 strips/petri dish[15]



(Fig.- 1: Cutting of rapid dissolving film from each petri dish)

2.2 Method of Preparation

Rapid dissolving films containing GSH were prepared using solvent casting method. An aqueous solution of polymer was prepared in distilled water. For preparing the solution, polymer was soaked in water for some time (wherever required). This was followed by addition of GSH in the aqueous solution of the polymer. Now, plasticizer (PEG 400 and/or Glycerol), sweetening agent (Aspartame and/or Sucralose), citric acid and flavor were also added to this solution. This solution was cast on a 9.6 cm diameter petri dish, containing a lining of liquid mercury (for leveling purpose). It was then dried at room temperature for 24 hours. The film was carefully removed from the petri dishes, checked for imperfections, and cut to the desired size (3x2 cm^2) to deliver the equivalent dose per strip. The strips were packed individually into aluminium foil and stored in a desiccator for further analysis.

For preparing rapid dissolving films, varying amount of polymer(s) was taken. Amount of plasticizer(s), sweetening agent(s), citric acid and flavor(s) were also varied to prepare films with desired properties.

2.3 Determination of *In-Vitro* Disintegration Time (DT)

In-vitro disintegration time (DT) of the prepared rapid dissolving films was determined visually in a glass beaker containing 50ml water and swirling every 10 seconds. Average of 3 films was taken for this purpose.

(Fig.-2: Disintegration of rapid dissolving film: Initial, during disintegration, complete disintegration)

2.4 Determination of *In-Vivo* Disintegration Time

In-vivo DT of the prepared rapid dissolving film was determined by mouth in three human volunteers. A rapid dissolving film was placed on the tongue of the volunteers and the time required to for disintegration of rapid dissolving film in the mouth was recorded.

2.5 Evaluation of Taste

Evaluation of taste was done by a taste panel with 2mg drug and subsequently one film held in the mouth for 10-15 seconds. The volunteers were asked to spit out, and the bitterness level was recorded. Volunteers were asked to gargle with distilled water before and after each taste evaluation. The taste of the rapid dissolving film was rated on a scale from 1 to 5. Scale 1 was equal to no taste and 5 was equivalent to too much of the respective taste.

1 = no bitter taste

2 = very slightly bitter

3 = slightly bitter

4 = moderately bitter

5 = bitter (equivalent to pure drug)

3. FILM FORMER

3.1 Formulation of rapid dissolving film using Pullulan as film former

For preparing rapid dissolving films, varying amount of Pullulan was taken. Amount of plasticizer (PEG 400 and/or glycerol), sweetening agent (Aspartame and/or Sucralose), citric acid and flavor (Passion fruit or lemon flavor) were also varied to prepare films with desired properties.

3.2 Formulation of rapid dissolving film using Methocel K3 Premium Hydroxyl Propyl Methylcellulose (Metho K3P) as film former

For preparing rapid dissolving films, varying amount of METHO K3P was taken. Amount of plasticizer (PEG 400 and/or glycerol), sweetening agent (Aspartame and/or Sucralose), citric acid and flavor (Passion fruit or lemon flavor) were also varied to prepare films with desired properties.

3.3 Formulation of rapid dissolving film using Methocel E3 Premium Hydroxyl Propyl Methylcellulose (Metho E3P) as film former

For preparing rapid dissolving films, varying amount of METHO E3P was taken. Amount of plasticizer (PEG 400 and/or glycerol), sweetening agent (Aspartame and/or Sucralose), citric acid and flavor (Passion fruit or lemon flavor) were also varied to prepare films with desired properties.

4. RESULT AND DISCUSSION:

4.1 Formulation of rapid dissolving film using Pullulan as film former

4.1.1 Optimization of Amount of Polymer (Pullulan)

Table 2: Optimization of Amount of Polymer - Pullulan

Formulation Code	Amount of Pullulan (mg)	Amount of water (ml)	Result
TPAP 1	200	20	No film
TPAP 2	300	20	No film
TPAP 3	400	20	Very thin film
TPAP 4	500	20	Film formed
TPAP 5	600	20	Thick film

*500 mg of Pullulan was taken for film formation in further studies.

4.1.2 Optimization of Amount of Plasticizer (PEG 400/ Glycerol) for Pullulan

4.1.2.1 Optimization of amount of PEG 400 alone as plasticizer for Pullulan

Table 3: Optimization of amount of PEG 400 alone as plasticizer for Pullulan

Formulation Code	Amount of Pullulan (mg)	Amount of PEG 400 (mg)	Amount of water (ml)	Result
TPAPEG 1	500	25	20	Brittle film
TPAPEG 2	500	50	20	Brittle film
TPAPEG 3	500	75	20	Film is not flexible
TPAPEG 4	500	100	20	Less Flexible film
TPAPEG 5	500	150	20	Flexible film
TPAPEG 6	500	200	20	Flexible film

* 150 mg of PEG400 alone was taken as plasticizer for Pullulan in further studies.

4.1.3 Optimization of amount of Glycerol alone as plasticizer for Pullulan

Table 4: Optimization of amount of Glycerol alone as plasticizer for Pullulan

Formulation Code	Amount of Pullulan (mg)	Amount of Glycerol (mg)	Amount of water (ml)	Result
TPAGL 1	500	25	20	Brittle film
TPAGL 2	500	50	20	Film is not flexible
TPAGL 3	500	75	20	Less flexible film
TPAGL 4	500	100	20	Flexible film
TPAGL 5	500	150	20	Flexible film
TPAGL6	500	200	20	Flexible but sticky film

* 100 mg of Glycerol alone was taken as plasticizer for Pullulan in further studies.

4.1.4 Optimization of amount of combination of PEG 400 and Glycerol as plasticizer for Pullulan

Table 5: Optimization of amount of combination of PEG 400 and Glycerol as plasticizer for Pullulan

Formulation Code	Amount of Pullulan (mg)	Amount of PEG 400 (mg)	Amount of Glycerol (mg)	Amount of water (ml)	Result
TPAPGL 1	500	25	50	20	Less flexible film
TPAPGL 2	500	25	75	20	Less flexible film
TPAPGL 3	500	50	50	20	Less flexible film
TPAPGL 4	**500**	**50**	**75**	**20**	**Flexible film**
TPAPGL 5	500	75	50	20	Less flexible film
TPAPGL6	500	75	75	20	Sticky film
TPAPGL 7	**500**	**100**	**50**	**20**	**Flexible film**
TPAPGL8	500	100	75	20	Sticky film

* Two combinations (a) 50 mg of PEG400 + 75 mg of Glycerol and (b) 100 mg of PEG400 + 50mg of Glycerol were taken as plasticizer for Pullulan in further studies.

4.1.5 Formulation of Rapid dissolving film using Pullulan as polymer

Based upon various trial batches, total eight formulations (P01 – P08) were designed for preparation of rapid dissolving film using Pullulan as film former.

Table 6: Formulation of rapid dissolving film using Pullulan as polymer

Formulation / Ingredients	P01	P02	P03	P04	P05	P06	P07	P08
Pullulan (mg)	500	500	500	500	500	500	500	500
GSH (mg)	27	27	27	27	27	27	27	27
PEG 400 (mg)	150	150	-	-	50	50	100	100
Glycerol (mg)	-	-	100	100	75	75	50	50
Aspartame (mg)	25	-	25	-	15	15	15	15
Sucralose (mg)	-	25	-	25	10	15	10	15
Citric acid (mg)	-	-	20	25	25	30	25	25
Passion fruit (ml)	-	-	0.1	-	-	0.1	0.1	-
Lemon flavor (ml)	-	0.1	-	0.1	0.1	-	-	0.1
Distilled Water (ml)	20	20	20	20	20	20	20	20
In-vitro DT (sec.)	45	46	40	42	48	45	51	52
In-vivo DT (sec.)	42	40	35	36	40	39	48	50
Taste	4	4	2	3	3	2	3	3

*Based upon parameters like disintegration time, taste etc, two formulations i.e., P03 and P06 were found to be optimum for preparation of rapid dissolving film using Pullulan as film former. So, these two films were further studied for various parameters.

4.2 Formulation of rapid dissolving film using Methocel K3 Premium Hydroxyl Propyl Methylcellulose (Metho K3P) as film former

4.2.1 Optimization of Amount of Polymer (METHO K3P)

Table 7: Optimization of Amount of Polymer - METHO K3P

Formulation Code	Amount of METHO K3P (mg)	Amount of water (ml)	Result
TMK3PAP 1	300	20	No film
TMK3PAP 2	400	20	No film
TMK3PAP 3	500	20	Very thin film
TMK3PAP 4	600	20	Film formed
TMK3PAP 5	700	20	Thick film

* 600 mg of METHO K3P was taken for film formation in further studies.

4.2.1.1Optimization of Amount of Plasticizer (PEG 400/ Glycerol) for METHO K3P

4.2.1.2 Optimization of amount of PEG 400 alone as plasticizer for METHO K3P

Table 8: Optimization of amount of PEG 400 alone as plasticizer for METHO K3P

Formulation Code	Amount of METHO K3P (mg)	Amount of PEG 400 (mg)	Amount of water (ml)	Result
TMK3PAPEG 1	600	25	20	Brittle film
TMK3PAPEG 2	600	50	20	Brittle film
TMK3PAPEG 3	600	75	20	Less flexible film
TMK3PAPEG 4	600	100	20	Flexible film
TMK3PAPEG 5	600	150	20	Flexible film
TMK3PAPEG 6	600	200	20	Flexible film but sticky

* 100 mg of PEG400 alone was taken as plasticizer for METHO K3P in further studies.

4.2.2 Optimization of amount of Glycerol alone as plasticizer for METHO K3P

Table 9: Optimization of amount of Glycerol alone as plasticizer for METHO K3P

Formulation Code	Amount of METHO K3P (mg)	Amount of Glycerol (mg)	Amount of water (ml)	Result
TMK3PAGL 1	600	25	20	Brittle film
TMK3PAGL 2	600	50	20	Film is not flexible
TMK3PAGL 3	600	75	20	Flexible film
TMK3PAGL 4	600	100	20	Flexible film
TMK3PAGL 5	600	150	20	Flexible film
TMK3PAGL6	600	200	20	Flexible but sticky film

* 75 mg of Glycerol alone was taken as plasticizer for METHO K3P in further studies.

4.2.3 Optimization of amount of combination of PEG 400 and Glycerol as plasticizer for METHO K3P

Table 10: Optimization of amount of combination of PEG 400 and Glycerol as plasticizer for METHO K3P

Formulation Code	Amount of METHO K3P (mg)	Amount of PEG 400 (mg)	Amount of Glycerol (mg)	Amount of water (ml)	Result
TMK3PAPGL 1	600	25	25	20	Less flexible film
TMK3PAPGL 2	600	25	50	20	Less flexible film
TMK3PAPGL 3	600	50	25	20	Less flexible film
TMK3PAPGL 4	**600**	**50**	**50**	**20**	**Flexible film**
TMK3PAPGL 5	**600**	**75**	**25**	**20**	**Flexible film**
TMK3PAPGL6	600	75	50	20	Flexible film but sticky
TMK3PAPGL 7	600	100	25	20	Sticky film
TMK3PAPGL8	600	100	50	20	Sticky film

* Two combinations (a) 50 mg of PEG400 + 50 mg of Glycerol and (b) 75 mg of PEG400 + 25mg of Glycerol were taken as plasticizer for METHO K3P in further studies.

4.2.4Formulation of rapid dissolving film using METHO K3P as polymer

Based upon various trial batches, total eight formulations (MK3P01 – MK3P08) were designed for preparation of rapid dissolving film using METHO K3P as film former.

Table 11: Formulation of rapid dissolving film using METHO K3P as polymer

Formulation / Ingredients	MK3P01	MK3P02	MK3P03	MK3P04	MK3P05	MK3P06	MK3P07	MK3P08
METHO K3P (mg)	600	600	600	600	600	600	600	600
GSH (mg)	27	27	27	27	27	27	27	27
PEG 400 (mg)	100	100	-	-	50	50	75	75
Glycerol (mg)	-	-	75	75	50	50	25	25
Aspartame (mg)	25	-	25	-	15	15	15	15
Sucralose (mg)	-	25	-	25	10	15	10	15
Citric acid (mg)	-	-	20	25	25	30	25	25
Passion fruit (ml)	-	-	0.1	-	0.1	-	0.1	-
Lemon flavor (ml)	-	0.1	-	0.1	-	0.1	-	0.1
Distilled Water (ml)	20	20	20	20	20	20	20	20
In-vitro DT (sec.)	42	41	35	35	30	28	45	38
In-vivo DT (sec.)	38	40	28	30	35	34	40	40
Taste	4	4	3	2	3	2	2	3

* Based upon parameters like disintegration time, taste etc, two formulations i.e., MK3P04 and MK3P06 were found to be optimum for preparation of rapid dissolving film using METHO K3P as film former. So, these two films were further studied for various parameters.

4.3 Formulation of rapid dissolving film using Methocel E3 Premium Hydroxyl Propyl Methylcellulose (METHO E3P) as film former

4.3.1 Optimization of Amount of Polymer (METHO E3P)

Table 12: Optimization of Amount of Polymer - METHO E3P

Formulation Code	Amount of METHO E3P (mg)	Amount of water (ml)	Result
TME3PAP 1	300	20	No film
TME3PAP 2	400	20	Very thin film
TME3PAP 3	500	20	Film formed
TME3PAP 4	600	20	Thick film
TME3PAP 5	700	20	Thick film

* 500 mg of METHO E3P was taken for film formation in further studies.

4.3.1.1Optimization of Amount of Plasticizer (PEG 400/ Glycerol) for METHO E3P

4.3.1.2 Optimization of amount of PEG 400 alone as plasticizer for METHO E3P

Table 13: Optimization of amount of PEG 400 alone as plasticizer for METHO E3P

Formulation Code	Amount of METHO E3P (mg)	Amount of PEG 400 (mg)	Amount of water (ml)	Result
TME3PAPEG 1	500	25	20	Brittle film
TME3PAPEG 2	500	50	20	Brittle film
TME3PAPEG 3	500	75	20	Less flexible film
TME3PAPEG 4	500	100	20	Flexible film
TME3PAPEG 5	500	125	20	Flexible film
TME3PAPEG 6	500	150	20	Flexible film but sticky

* 100 mg of PEG400 alone was taken as plasticizer for METHO E3P in further studies.

4.3.2 Optimization of amount of Glycerol alone as plasticizer for METHO E3P

Table 14: Optimization of amount of Glycerol alone as plasticizer for METHO E3P

Formulation Code	Amount of METHO E3P (mg)	Amount of Glycerol (mg)	Amount of water (ml)	Result
TME3PAGL 1	500	25	20	Brittle film
TME3PAGL 2	500	50	20	Film is not flexible
TME3PAGL 3	500	75	20	Less flexible film
TME3PAGL 4	500	100	20	Flexible film
TME3PAGL 5	500	150	20	Flexible film
TME3PAGL6	500	200	20	Flexible but sticky film

*100 mg of Glycerol alone was taken as plasticizer for METHO E3P in further studies.

4.3.3 Optimization of amount of combination of PEG 400 and Glycerol as plasticizer for METHO E3P

Table 15: Optimization of amount of combination of PEG 400 and Glycerol as plasticizer for METHO E3P

Formulation Code	Amount of METHO E3P (mg)	Amount of PEG 400 (mg)	Amount of Glycerol (mg)	Amount of water (ml)	Result
TME3PAPGL 1	500	25	25	20	Less flexible film
TME3PAPGL 2	500	25	50	20	Less flexible film
TME3PAPGL 3	**500**	**25**	**75**	**20**	**Flexible film**
TME3PAPGL 4	500	50	25	20	Less flexible film
TME3PAPGL 5	**500**	**50**	**50**	**20**	**Flexible film**
TME3PAPGL6	500	50	75	20	sticky film
TME3PAPGL 7	500	75	25	20	Less flexible film
TME3PAPGL8	500	75	50	20	Sticky film

* Two combinations (a) 25 mg of PEG400 + 75 mg of Glycerol and (b) 50 mg of PEG400 + 50mg of Glycerol were taken as plasticizer for METHO E3P in further studies.

4.3.4 Formulation of rapid dissolving film using METHO E3P as polymer

Based upon various trial batches, total eight formulations (ME3P01 – ME3P08) were designed for preparation of rapid dissolving film using METHO E3P as film former.

Table 16: Formulation of rapid dissolving film using METHO E3P as polymer

Formulation / Ingredients	ME3P01	ME3P02	ME3P03	ME3P04	ME3P05	ME3P06	ME3P07	ME3P08
METHO E3P (mg)	600	600	600	600	600	600	600	600
GSH (mg)	27	27	27	27	27	27	27	27
PEG 400 (mg)	100	100	-	-	50	50	25	25
Glycerol (mg)	-	-	100	100	50	50	75	75
Aspartame (mg)	25	-	25	-	15	15	15	15
Sucralose (mg)	-	25	-	25	10	15	10	15
Citric acid (mg)	-	25	20	25	25	30	25	25
Passion fruit (ml)	-	0.1	-	0.1	-	0.1	0.1	-
Lemon flavor (ml)	-	-	0.1	-	0.1	-	-	0.1
Distilled Water (ml)	20	20	20	20	20	20	20	20
In-vitro DT (sec.)	35	37	36	40	34	35	37	36
In-vivo DT (sec.)	37	33	40	40	35	32	35	37
Taste	4	2	3	2	3	2	3	3

* Based upon parameters like disintegration time, taste etc, two formulations i.e., ME3P02 and ME3P06 were found to be optimum for preparation of rapid dissolving film using METHO E3P as film former. So, these two films were further studied for various parameters.

4.4 Formulation of rapid dissolving film using Methocel E15 Premium Hydroxyl Propyl Methylcellulose (METHO E15P) as film former

4.4.1 Optimization of Amount of Polymer (METHO E15P)

Table 17: Optimization of Amount of Polymer - METHO E15P

Formulation Code	Amount of METHO E15P (mg)	Amount of water (ml)	Result
TME15PAP 1	300	20	Very thin film
TME15PAP 2	400	20	Film formed
TME15PAP 3	500	20	Film formed
TME15PAP 4	600	20	Thick film
TME15PAP 5	700	20	Thick film

* 400 mg of METHO E15P was taken for film formation in further studies.

4.4.2 Optimization of Amount of Plasticizer (PEG 400/ Glycerol) for METHO E15P

4.4.2.1 Optimization of amount of PEG 400 alone as plasticizer for METHO E15P

Table 18: Optimization of amount of PEG 400 alone as plasticizer for METHO E15P

Formulation Code	Amount of METHO E15P (mg)	Amount of PEG 400 (mg)	Amount of water (ml)	Result
TME15PAPEG 1	400	10	20	Brittle film
TME15PAPEG 2	400	25	20	Brittle film
TME15PAPEG 3	400	50	20	Flexible film
TME15PAPEG 4	400	75	20	Flexible film
TME15PAPEG 5	400	100	20	Flexible film but sticky
TME15PAPEG 6	400	125	20	Flexible film but sticky

* 50 mg of PEG400 alone was taken as plasticizer for METHO E15P in further studies.

4.4.3 Optimization of amount of Glycerol alone as plasticizer for METHO E15P

Table 19: Optimization of amount of Glycerol alone as plasticizer for METHO E15P

Formulation Code	Amount of METHO E15P (mg)	Amount of Glycerol (mg)	Amount of water (ml)	Result
TME15PAGL 1	400	10	20	Brittle film
TME15PAGL 2	400	25	20	Film is not flexible
TME15PAGL 3	400	50	20	Less flexible film
TME15PAGL 4	400	75	20	Flexible film
TME15PAGL 5	400	100	20	Flexible film
TME15PAGL 6	400	150	20	Flexible film but brittle

* 75 mg of Glycerol alone was taken as plasticizer for METHO E15P in further studies.

4.4.4 Optimization of amount of combination of PEG 400 and Glycerol as plasticizer for METHO E15P

Table 20: Optimization of amount of combination of PEG 400 and Glycerol as plasticizer for METHO E15P

Formulation Code	Amount of METHO E15P (mg)	Amount of PEG 400 (mg)	Amount of Glycerol (mg)	Amount of water (ml)	Result
TME15PAPGL 1	400	20	30	20	Less flexible film
TME15PAPGL 2	400	20	40	20	Less flexible film
TME15PAPGL 3	**400**	**20**	**50**	**20**	**Flexible film**
TME15PAPGL 4	**400**	**30**	**30**	**20**	**Flexible film**
TME15PAPGL 5	400	30	40	20	Flexible film
TME15PAPGL6	400	30	50	20	sticky film
TME15PAPGL 7	400	40	30	20	Less flexible film
TME15PAPGL8	400	40	40	20	Sticky film

* Two combinations (a) 20 mg of PEG400 + 50 mg of Glycerol and (b) 30 mg of PEG400 + 30mg of Glycerol were taken as plasticizer for METHO E15P in further studies.

4.4.5 Formulation of rapid dissolving film using METHO E15P as polymer

Based upon various trial batches, total eight formulations (ME15P01 – ME15P08) were designed for preparation of rapid dissolving film using METHO E15P as film former.

Table 21: Formulation of rapid dissolving film using METHO E15P as polymer

Formulation / Ingredients	ME15P01	ME15P02	ME15P03	ME15P04	ME15P05	ME15P06	ME15P07	ME15P08
METHO E15P (mg)	400	400	400	400	400	400	400	400
GSH (mg)	27	27	27	27	27	27	27	27
PEG 400 (mg)	50	50	-	-	20	20	30	30
Glycerol (mg)	-	-	75	75	50	50	30	30
Aspartame (mg)	20	-	20	-	10	10	15	15
Sucralose (mg)	-	20	-	20	10	10	05	05
Citric acid (mg)	-	20	15	20	20	25	20	25
Passion fruit (ml)	-	0.1	-	0.1	-	0.1	-	0.1
Lemon flavor (ml)	-	-	0.1	-	0.1	-	0.1	-
Distilled Water (ml)	20	20	20	20	20	20	20	20
In-vitro DT (sec.)	34	35	37	39	40	39	38	36
In-vivo DT (sec.)	35	37	42	41	43	41	34	38
Taste	4	2	3	2	3	3	3	2

* Based upon parameters like disintegration time, taste etc, two formulations i.e., ME5P02 and ME5P08 were found to be optimum for preparation of rapid dissolving film using METHO E15P as film former. So, these two films were further studied for various parameters.

4.4.6 Formulation of rapid dissolving film using POLYOX WSR N10 (POLY N10) as film former

4.4.6.1 Optimization of Amount of Polymer (POLY N10)

Table 22: Optimization of Amount of Polymer - POLY N10

Formulation Code	Amount of POLY N10 (mg)	Amount of water (ml)	Result
TPN10AP 1	300	20	No film
TPN10AP 2	400	20	Very thin film
TPN10AP 3	500	20	Film formed
TPN10AP 4	600	20	Thick film
TPN10AP 5	700	20	Thick film

* 500 mg of POLY N10 was taken for film formation in further studies.

4.4.6.2 Optimization of Amount of Plasticizer (PEG 400/ Glycerol) for POLY N10

4.4.6.3 Optimization of amount of PEG 400 alone as plasticizer for POLY N10

Table 23: Optimization of amount of PEG 400 alone as plasticizer for POLY N10

Formulation Code	Amount of POLY N10 (mg)	Amount of PEG 400 (mg)	Amount of water (ml)	Result
TPN10APEG 1	500	25	20	Brittle film
TPN10APEG 2	500	50	20	Less Flexible film
TPN10APEG 3	500	75	20	Flexible film
TPN10APEG 4	500	100	20	Flexible film
TPN10APEG 5	500	150	20	Flexible film but sticky

* 75 mg of PEG400 alone was taken as plasticizer for POLY N10 in further studies.

4.4.6.3 Optimization of amount of Glycerol alone as plasticizer for POLY N10

Table 24: Optimization of amount of Glycerol alone as plasticizer for POLY N10

Formulation Code	Amount of POLY N10 (mg)	Amount of Glycerol (mg)	Amount of water (ml)	Result
TPN10AGL 1	500	25	20	Brittle film
TPN10AGL 2	500	50	20	Film is not flexible
TPN10AGL 3	500	75	20	Less flexible film
TPN10AGL 4	500	100	20	Flexible film
TPN10AGL 5	500	150	20	Flexible film
TPN10AGL6	500	200	20	Flexible but sticky film

* 100 mg of Glycerol alone was taken as plasticizer for POLY N10 in further studies.

4.4.6.4 Optimization of amount of combination of PEG 400 and Glycerol as plasticizer for POLY N10

Table 25: Optimization of amount of combination of PEG 400 and Glycerol as plasticizer for POLY N10

Formulation Code	Amount of POLY N10 (mg)	Amount of PEG 400 (mg)	Amount of Glycerol (mg)	Amount of water (ml)	Result
TPN10APGL 1	500	25	25	20	Less flexible film
TPN10APGL 2	**500**	**25**	**50**	**20**	**Flexible film**
TPN10APGL 3	500	25	75	20	Flexible film
TPN10APGL 4	**500**	**50**	**25**	**20**	**Flexible film**
TPN10APGL5	500	50	50	20	Flexible film
TPN10APGL6	500	50	75	20	Sticky film

* Two combinations (a) 25 mg of PEG400 + 50 mg of Glycerol and (b) 50 mg of PEG400 + 25mg of Glycerol were taken as plasticizer for POLY N10 in further studies.

4.4.7 Formulation of rapid dissolving film using POLY N10 as polymer

Based upon various trial batches, total eight formulations (PN01 – PN08) were designed for preparation of rapid dissolving film using POLY N10 as film former.

Table 26: Formulation of rapid dissolving film using POLY N10 as polymer

Formulation / Ingredients	PN01	PN02	PN03	PN04	PN05	PN06	PN07	PN08
POLY N10 (mg)	500	500	500	500	500	500	500	500
GSH (mg)	27	27	27	27	27	27	27	27
PEG 400 (mg)	75	75	-	-	25	25	50	50
Glycerol (mg)	-	-	100	100	50	50	25	25
Aspartame (mg)	25	-	25	-	15	15	15	15
Sucralose (mg)	-	25	-	25	10	15	10	15
Citric acid (mg)	-	-	20	25	25	30	25	25
Passion fruit (ml)	-	0.1	-	0.1	-	0.1	-	0.1
Lemon flavor (ml)	-	-	0.1	-	0.1	-	0.1	-
Distilled Water (ml)	20	20	20	20	20	20	20	20
In-vitro DT (sec.)	25	26	28	27	20	30	23	22
In-vivo DT (sec.)	27	25	30	29	25	28	25	24
Taste	4	3	3	3	2	2	3	2

* Based upon parameters like disintegration time, taste etc, two formulations i.e., PN05 and PN08 were found to be optimum for preparation of rapid dissolving film using POLY N10 as film former. So, these two films were further studied for various parameters.

4.5 FINAL FORMULA FOR FORMULATION OF RAPID DISSOLVING FILM USING VARIOUS POLYMERS AS FILM FORMER

Based upon above studies, following ten formulations were finalized as optimum for preparation of rapid dissolving film. These ten formulations were further studied for various parameters.

Table 27: Formulation of rapid dissolving film using various polymers as film former

Formulation Code	FF01	FF02	FF03	FF04	FF05	FF06	FF07	FF08	FF09	FF10
Formulation / Ingredients	P03	P06	MK3P04	MK3P06	ME3P02	ME3P06	ME15P02	ME15P08	PN05	PN08
PULLULAN (mg)	500	500	-	-	-	-	-	-	-	-
METHO K3P (mg)	-	-	600	600	-	-	-	-	-	-
METHO E3P (mg)	-	-	-	-	600	600	-	-	-	-
METHO E15P (mg)	-	-	-	-	-	-	400	400	-	-
POLY N10 (mg)	-	-	-	-	-	-	-	-	500	500
GSH (mg)	27	27	27	27	27	27	27	27	27	27
PEG 400 (mg)	-	50	-	50	100	50	50	30	25	50
Glycerol (mg)	100	75	75	50	-	50	-	30	50	25
Aspartame (mg)	25	15	-	15	-	15	-	15	15	15
Sucralose (mg)	-	15	25	15	25	15	20	05	10	15
Citric acid (mg)	20	30	25	30	25	30	20	25	25	25
Passion fruit (ml)	0.1	0.1	-	-	0.1	0.1	0.1	0.1	-	0.1
Lemon flavor (ml)	-	-	0.1	0.1	-	-	-	-	0.1	-
Distilled Water (ml)	20	20	20	20	20	20	20	20	20	20
In-vitro DT (second)	40	45	35	28	37	35	35	36	20	22
In-vivo DT (second)	35	39	30	34	33	32	37	38	25	24
Taste	2	2	2	2	2	2	2	2	2	2

4.6 FINAL FORMULA FOR FORMULATION OF RAPID DISSOLVING FILM OF ONDANSETRON HYDROCHLORIDE

Based upon various evaluation parameters of RDF of Granisetron hydrochloride, using various polymers and other excipients, two formulations were found to be optimum i.e. FF2 and FF8. So, combination of these polymers and other excipients were used to prepare RDF of Ondansetron hydrochloride (OFF1 and OFF2).

Table 28: Formulation of rapid dissolving film of Ondansetron hydrochloride

Formulation / Ingredients	OFF1	OFF2
PULLULAN (mg)	500	-
METHO E15P (mg)	-	400
OND (mg)	60	60
PEG 400 (mg)	50	30
Glycerol (mg)	75	30
Aspartame (mg)	15	15
Sucralose (mg)	15	05
Citric acid (mg)	30	25
Passion fruit (ml)	0.1	0.1
Distilled Water (ml)	20	20
In-vitro DT (second)	47	38
In-vivo DT (second)	42	37
Taste	2	2

5. CONCLUSION:

In the present work, mouth dissolving films containing Granisetron hydrochloride and Ondansetron hydrochloride were developed to dissolve immediately in mouth for fast drug action. The work included the development, characterization and evaluation of rapid dissolving films for dissolution in mouth and release the drug for rapid onset of action. Granisetron hydrochloride and Ondansetron hydrochloride were selected as model drugs for the study. Both the drugs are antiemetic. In emesis, quick drug action is required and intake of water is also not acceptable. So, rapid dissolving film of these two drugs were developed and evaluated. Rapid dissolving films of both the drugs Granisetron hydrochloride and Ondansetron hydrochloride were prepared using various polymers and other excipients that dissolve rapidly and release the drugs for rapid absorption.Solvent evaporation method was used for preparation of the film. Various polymers used in the study were: Pullulan, Metho K3P, Metho E3P, Metho E15P and Poly N10. PEG-400 and glycerol were used as plasticizer. Aspartame and sucralose were used as sweetening agent while citric acid was used as saliva stimulating agent. Passion fruit and lemon flavour were used as flavouring agent.

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