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FORMULATION AND EVALUATION OF ORAL MOUTH DISSOLVING FILM OF ANTIEMETICS DRUGS

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ABSTRACT

Fast dissolving oral films (FDOFS) are the most advanced form of oral solid dosage form due to more flexibility and comfort. It improve the effectiveness of dissolving film within minute in oral cavity after the contact with saliva as compared to fast dissolving film, without chewing and no need of water for administration. This is used in solid dispersion method with gum acacia at weight ratio of 1:4 showed excellent film forming characteristics such as disintegration time of 57 sec and percentage drug release 95.95% within 2 minutes. This study as formulation and evaluation the oral mouth dissolving film of Granisetron as used to treat in nausea, vomiting. The formulated by oral mouth dissolving film of Granisetron using suitable polymer like hydroxypropyl methyl cellulose (HPMC) and in combination with aspartame as sweetener sucrose, ascorbic acid as saliva stimulating agent, diethyl phthalate as plasticizer, and peppermint oil as a flavoring agent. The prepared films were evaluated in invitro drugs release.

KEYWORDS: Fast dissolving films, oral mucosa, solid dispersion method.

1.1. Oral route

A solid dosage form that dissolves or disintegrates quickly in the oral cavity resulting in solution or suspension without the need for administration of water is known as oral fast dispersing dosage form.[1]

Fast dissolving Oral Films (FDOF) are a solid single-unit dosage form which are made of a water dissolving polymer, allows the dosage form to rapidly hydrate, adhere and dissolve

when placed on the tongue in the oral cavity to provide local or systemic drug delivery. The large surface area available in the film dosage form allows rapid wetting by saliva, quick disintegration, dissolution and absorption of drug directly enter into the systemic circulation without undergoing first-pass hepatic metabolism with increased bioavailability. Some drugs are absorbed from mouth, pharynx and esophagus as the saliva passes down into the stomach. In such cases bioavailability of drug is significantly greater than those observed from conventional tablet dosage form.[2]

Mouth dissolving films, a new drug delivery system for the oral delivery of the drugs, was developed based on the technology of the transdermal patch.[3] Various film formers like Polyvinyl alcohol, Polyvinyl pyrrolidone (PVP), Maltodextrin, Hydroxy Propyl Methyl Cellulose (HPMC), Hydroxypropyl Cellulose (HPMC), Methyl Cellulose (MC), Sodium Carboxy Methyl Cellulose (Na CMC), Chitosan and some natural gums have been used in the production of films.[4] Oral route of drug administration has been one of the most convenient and accepted route of drug delivery and amongst it the intraoral route is the most preferred due to its convenience and rapid onset of action.[5]

Advantages

- Accessibility of larger surface area that leads to quickly disintegrate and dissolution in the oral cavity within seconds.
- Fast Dissolving Film is flexible so they are not as fragile and need not any kind of special package for protection during transportation and storage as compared to FDT.
- No need of water has led to better satisfactoriness amongst the dysphasic patients.
- No fear of chocking as compared to FDT.
- The large surface area available in the film dosage form allows rapid wet by saliva then quickly disintegrates and dissolve and absorbed directly and can enter the systemic circulation without undergoing first-pass hepatic metabolism and on increase the bioavailability
- The dosage form can be consumed at any place and any time as per convenience of the individual

Disadvantages

- Dose uniformity is a technical challenge
- Hygroscopic in nature
- High doses cannot be incorporated

- Require special packaging for products stability and safety.[6]

2. Saliva and Mucus

Salivary mucins have a number of host-defense functions including the establishment of a permeability barrier overlying the epithelia, lubrication of surface tissues and modulation of the colonization of oral microorganisms. Approximately 750 ml of saliva is produced daily in an adult with 60% from the submandibular glands, 30% from the parotids, 5% from the sublingual glands, and around 6% from the minor salivary glands found beneath the epithelium in most regions of the oral mucosa.[7] The extent to which such adhesion stimulates further flow of mucus from the occluded minor salivary glands is unclear. The mucus film may act as a further barrier to the absorption of drugs.[8]

3. Oral mucosal sites

Within the oral mucosal cavity, delivery of drugs is classified in to three categories.

1. Sublingual delivery: is the administration of the drug via the sublingual mucosa (the membrane of the ventral surface of the tongue and the floor of the mouth to the systemic circulation.

2. Buccal delivery: is the administration of drug via the buccal mucosa (the lining of the cheek) to the systemic circulation.

3. Local delivery: for the treatment of conditions of the oral cavity, principally ulcers, fungal conditions and periodontal disease. These oral mucosal sites differ greatly from one another in terms of anatomy, permeability to an applied drug and their ability to retain a delivery system for a desired length of time.[9]

4. MATERIAL AND METHOD

Formulation and Development

Formulation Mouth Dissolving Film Of Granisetron Hydrochloride

The preparation of mouth dissolving film of Granisetron hydrochloride by using solid dispersion method

Solid dispersions of Granisetron hydrochloride with gum acacia in the weight ratio of 1:4 were prepared using kneading technique. The appropriate weighed amounts of Granisetron hydrochloride and gum acacia were moistened with methanol to get homogenous slurry. Methanol was removed by vacuum evaporation. The resulting mass was transferred to

vacuum desicator and dried to constant weight. The dried product was pulverized and sifted through sieve # 80. The samples prior to be used for the study were stored in the desiccator.

5. Preparation of fast dissolving films

Accurately weighed quantities of film forming polymers such as HPMC of various grades, plasticizers, sweetener, salivary stimulating agent and flavoring agent were dissolved in distilled water and resulting dispersion was stirred for 90 min at 70°C. The mixture of solid dispersion was casted onto the glass mould or petri dish allowed to dry under vacuum for 24 hrs. After sufficient drying, film was carefully removed in petri dish and film was cut into 2×2 cm^2 strips. The prepared square thin film strips were stored in a desicator for further studies.

Table: Composition mouth dissolving film prepared by using different concentration of polymer hydroxypropyl methyl cellulose.

Sr. no	Content	F 1 (mg)	F 2 (mg)	F 3 (mg)	F 4 (mg)	Use of Ingredients
1	Granisetron HCL Equivalent to 10 mg (solid dispersion)	40	40	40	40	API
2	Hydroxypropyl methyl cellulose	190	200	205	210	Polymer
3	Diethyl phthalate	4ml	4ml	4ml	4ml	Plasticizer
4	Ascorbic acid	10mg	10mg	10mg	10mg	Salivary agent
5	Lactose	40mg	40mg	40mg	40mg	Sweetening agent
6	Sodium Starch glycolate	15mg	15mg	15mg	15mg	Superdisintegrant
7	menthol	Q.s	Q.s	Q.s	Q.s	Flavouring agent

6. Evaluation of prepared mouth dissolving film

1. Morphological properties

The properties such as homogenecity, color, transparency and surface of the oral film were evaluated by visually inspection. Result are reported in table no.8.

2. Visual appearance

The oral fast dissolving film were evaluated for the appearance as transparent.

3. Film thickness

A thickness of the film should be calculated by using micrometer screw gauge. Film should be measured at five positions i.e. central and the four corners and the mean thickness are calculated. This test should be performed on six films of each formulation maximum

variation in the thickness of the films should be less than 5% and mean ± S.D calculated. The thickness of the films maximum of less than 5%. Result are reported in table no.9.

4. Folding endurance

It is measured manually for the prepared oral film. A film was repeatedly folded at the same place till it broke. The number of times the film could be folded at the same place without breaking gave the value of folding endurance. This test should be performed on six films of each formulation and mean ± S.D calculated.[39] Result are reported in table no.10.

5. Disintegration test

The time for disintegration of ODTs is less than one minute. It ranges from 5-30 seconds based on patient conditions. Strip is examined using disintegration test apparatus. A basket sinker containing the tablets is placed just below the water surface in a container with 900 ML of water at 37 C, and a paddle rotating at 100 rpm used. Result are reported in table no.13.

6. Weight Uniformity

For each formulation, there randomly selected films were used. For weight variation test, 3 films from each batch were weighed individually and the average weight was calculated. Result are reported in table no.11.

7. Drug content uniformity of films

The films (2cm2) were cut and added to a beaker containing 100ml of phosphate buffer pH 6.8. The medium was stirred with magnetic bead. The contents were filtered using Whatsman filter paper and the filtrate was examined for the drug content against the reference solution consisting of placebo films at 244 nm spectrophotometrically.[2]Result are reported in table no 14.

8. Surface of PH

The film allowed to swell closed petridish at room temperature for 30 min in a10 ml phosphate buffer PH 6.8 and determined PH for using PH paper. Result are reported in table no.12.

9. Dissolution and in vitro drugs release

- Medium : phosphate buffer ph 6.8
- Volume : 900 ml

- Apparatus : USP type 1
- RPM : 50 rpm
- Alarm time: 10,20,30,40,50.sec.
- Volume of withdrawn : 5 ml
- Temperature : $37^0 \pm 0.5^o$ c
- ƛ maxima : 244 nm

The In vitro drug dissolution of films were performed using phosphate buffer pH 6.8.by using a paddle apparatus at a $37^0 \pm 0.5^o$ c and at 50 rpm. each square cut strip 2 cm x 2cm was placed in dissolution media. 5 ml Samples were collected periodically and replaced with a fresh dissolution medium. and sample was filtered through whatsman filter paper and sample is determined spectrophotometrically at 244 nm. (model UV-1800 UV- visible spectrophotometer, shimadzu, japan) Result are reported in table no.15.

7. RESULTS AND DISCUSSION

Morphology

The morphology of all film of formulation was found to be smooth and transparent, without any scratches and free from bubbles.

Table 8: Morphology of mouth dissolving film Granisetron HCL.

Sr. no	Formulation	Surface
1	F1	Smooth, Transparent
2	F2	Smooth, Transparent
3	F3	Smooth, Transparent
4	F4	Smooth, Transparent

2. Visual appearance

The visual appearance of formulation was found to be semitransparent film hydoxypropyl methyl cellulose was used as a plasticizer and film was free from bubbles.

Fig: Visual Appearance Of Film Formulation F1,F2,F3,F4.

3. Thickness Of film

The thickness film polymer was measured found to be 0.13-0.22 mm. it is good film property. And the thickness of film is depend on the use of concentration of polymer.

Table 9: Thickness Of Mouth Dissolving Film Of Granisetrone Hcl.

Sr. no.	Formulations	Thickness in mm ± S.D
1	F1	0.13 ± 0.9
2	F2	0.15 ± 0.12
3	F3	0.18 ± 0.15
4	F3	0.22 ± 0.6

4. Folding endurance

The folding endurance the film was measured manually. The all formulation was fond to be more than 355 time which was good film properties of all formulation. And folding endurance depend for concentration of plasticizer and polymer. Result was reported table no.10.

Table: Folding Endurance Of MDF Of Granisetron Hcl.

Sr. no.	Formulation	Folding endurance
1	F1	> 355
2	F2	> 355
3	F3	> 355
4	F4	> 355

5. Weight variation

The was films was found to be in the range 181.2 mg to 206.5 mg. the result was found to table no.11.

Table: **Weight Variation Of MDF Of Granisetron Hcl.**

Sr. no.	Formulation	Weight in mg ± S.D
1	F1	187.3 ± 0.223
2	F2	192.7 ± 0. 415
3	F3	199.1 ± 0.646
4	F4	203.4 ± 0. 758

6. Surface of PH

The PH is observed all formulation between 6.0. to 6.8. the PH range between 6.0 to 6.8 is all formulation PH near by saliva. Result was reported table no.12.

Table: Surface Of PH MDF Of Granisetron Hcl.

Sr. no.	Formulation	Surface pH
1	F1	6.2 ± 0.23
2	F2	6.5 ± 0.18
3	F3	6.8 ± 0.12
4	F4	6.7 ± 0.25

7. Disintegration time

The disintegration time of all formulation of films was observed between the 25 to 17 sec. and it is used in superdisintgrant of sodium starch glycolate. It is observed in decreased in disintegration time.

Table No. 13: Disintegration Time of Granisetron Hcl.

Sr. no	Formulation	Disintegration time (sec)
1	F_1	25 ± 1.55
2	F_2	21 ± 1.88
3	F_3	19 ± 1.09
4	F_4	17 ± 2.05

8. Drugs Content Uniformity

The average values of drugs content uniformity was found to be range of 87.15% ± 055 to 108.3 ± 0.89. the result is prepared film of the study was capable of producing film are uniform drugs content.

Table: Drugs Content Of MDF Granisetron Hcl.

Sr. no	Formulation	% drugs content
1	F1	99.34 % ± 0.89
2	F2	98.22 % ± 0.59
3	F3	93.65 % ± 0.33
4	F4	87.15 % ± 0.55

9. In Vitro Drugs Release Study

The dissolution study all formulations performed in phosphate buffer PH 6.8 as dissolution medium by using USP type I dissolution apparatus. The % cumalative drugs release of all formulation oral mouth dissolving film of Granisetron HCL is given table no.16 and their comparative drugs release profile is fig.

Table: % Drugs Release Of Granisetron Hcl.

Sr. no	Time (sec)	% Drugs Release			
		F1	F2	F3	F4
1	0	0.00	0.00	0.00	0.00
2	10	82.9 ± 0.55	79.9 ± 0.22	79.0 ± 0.67	76.3 ± 0.82
3	20	84.6 ± 0.88	83.6 ± 0.42	81.4 ± 0.47	79.4 ±0. 35
4	30	84.9 ± 0.69	85.8 ± 0.48	82.5 ± 0.88	83.9 ± 0.76
5	40	87.4 ± 0.93	86.9 ± 0.85	86.4 ± 0.55	85.3 ± 0.61
6	50	93.4 ± 0.81	91.4 ± 0.107	95.4 ± 0.67	94.3 ± 0.44

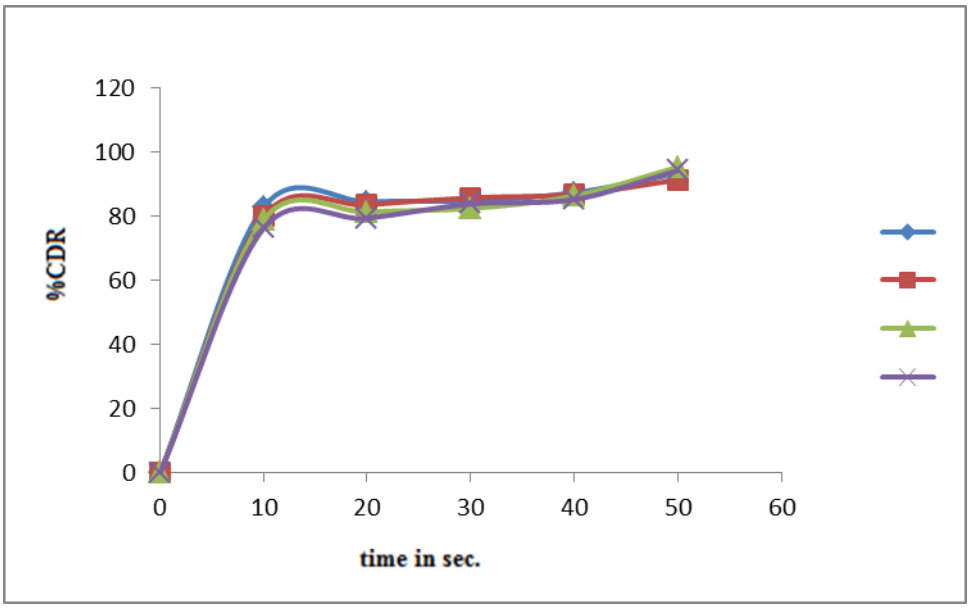

Figure: In-vitro Drugs Release of F1, F2, F3 & F4.

The comparing dissolution profile of formulation F1, F2, F3, F4, using of plasticizer diethyl phthalate is concentration is constant and hydroxypropylmethyl cellulose is increased for F1 to F4 formulations. It is a observed percent drugs release was the order of F1>F2>F3> F4. the release was found to be 94.3% for F4.

8. CONCLUSION

- The mouth dissolving film of granisetron hydrochloride by using a solid dispersion method was successfully prepared.
- The prepared film was smooth and transparent.
- This is prepared film is evaluated in visual appearance, film thickness, folding endurance, weight uniformity, PH of surface disintegration test, in vitro drugs release study.
- The batch no.4 is optimized batch because of % drugs release is increased of batch no.4 and disintegration time is increased.

- All parameter were will within limit of official book indicated suitability of the method with showing industrial applicability of the formulation.

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