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FORMULATION DEVELOPMENT AND EVALUATION OF ORAL THIN FILMS- DIPHEN HYDRAMINE HCl

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ABSTRACT: The aim of this study was to develop a fast releasing oral polymeric thin film, prepared by solvent casting method, with good mechanical properties, instant disintegration and dissolution. Diphenhydramine hydrochloride, an antihistamine drug belonging to BCS class I was used for oral thin film preparation. The formulations from the preliminary trial were analyzed which was applied to optimize the type of polymers (Gelatin and HPMC E15), concentration of polymers, plasticizer (Glycerol, Propylene Glycol, PEG 400), surfactant (TWEEN 80) and sweetener (Mannitol).The resultant films were evaluated for thickness, folding endurance, drug content, Surface pH, in vitro disintegration time, in vitro dissolution studies .Oral thin films which were prepared with surfactant showed better results i.e., good disintegrating and dissolution properties than without surfactant. The optimized film disintegrated in less than 30s, releasing more than 90% of drug within 90sec.

INTRODUCTION: Oral thin film is a dosage form containing medicinal substances which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue" [1].

It employs water dissolving polymer which is a hydrocolloid which may be bio adhesive polymer which allows the dosage form to quickly hydrate, adhere, dissolve when placed on the tongue or the oral cavity to provide rapid local and systemic drug delivery [2]. Due to rapid dissolving of the film, the term soluble film is preferred by FDA, whereas the European Medicines Agency is using orodispersible film [3].

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Oral polymeric thin films are the most advanced form of oral solid dosage forms due to more flexibility and comfort. It improves the efficacy of the active pharmaceutical ingredients by dissolving within minute in oral cavity after the contact with less saliva as compared to the fast dissolving tablets, without chewing and no need of water for the administration [4].

Oral films are preferred by patients suffering from dysphasia, motion sickness, repeated emesis and mental disorders since they are unable to swallow large amounts of water with dosage forms. The advantages of convenient dosing and portability of oral films have led to a wide applicability of this dosage form in pediatric as well as geriatric patients. The drug used is Diphenhydramine Hydrochloride which is a histamine H1 antagonist and used as an antiemetic, antitussive, for dermatoses and pruritus, for hypersensitivity reactions, as an ingredient in common cold preparations [5].

The polymers used are gelatin and HPMCE15. Gelatin is a natural polymer available. Under specific conditions (temperature, solvent, pH) gelatin macromolecules can display flexibility sufficient to realize a wide variety of conformations. HPMC E15 is another polymer used due to its greater disintegration, dissolution and good film forming properties. The important step involved during dissolution of a hydrophilic polymer include absorption of water on polymer, breaking of polymer bonds with a simultaneous creation of water polymer bonds, separation of polymer chains, swelling and finally dispersion of polymer chains in medium [6].

The main aim of the present study was to prepare oral thin film of Diphenhydramine HCl for rapid dissolution in oral cavity. The films were prepared by solvent casting method and evaluated. This study optimizes the type, concentration of polymer and also optimizes the plasticizer and its concentration.

MATERIALS AND METHOD:

Materials: Gelatin, HPMC E-15, Ethanol, Tween80, Mannitol, Propylene glycol, Glycerol, PEG 400, Millipore Water. All reagents are of analytical grade.

Preparation of Oral Thin Films:

Solvent casting method [7]**:** Oral thin films were prepared by dissolving the polymer (Gelatin or HPMC) in solvent mixture (Millipore water and Ethanol), with continuous stirring Drug, Mannitol is added. To the resulting solution plasticizers (Glycerol, PEG 400, Propylene glycol) and surfactants (Tween 80) are added subsequently and stirred for 15 minutes. These solutions were casted slowly on to a glass plate of diameter 5cm without formation of air bubbles. (Each strip 2*2 cm^2 consists of 30mg of drug) These plates were kept aside for 48 hrs and dried films are carefully separated from the plate and evaluated. Various formulations were prepared as per **table 1 & 2.**

TABLE 1: FORMULATIONS WITHOUT SURFACTANT

Formulation code	API 150mg	Polymer	Plasticizer	Water	Ethanol	Sweetener
F1	"	Gelatin 50mg	Glycerol 0.1ml	q.s	Ethanol 1ml	Mannitol 0.5mg
F2	"	60mg	Glycerol 0.1ml	q.s	"	"
F3	"	70mg	Glycerol 0.1ml	q.s	"	"
F4	"	80mg	Glycerol 0.1ml	q.s	"	"
F5	"	90mg	Glycerol 0.1ml	q.s	"	"
F6	"	100mg	Glycerol 0.1ml	q.s	"	"
F7	"	150mg	Glycerol 0.1ml	q.s	"	"
F8	"	"	0.2ml	q.s	"	"
F9	"	"	0.4ml	q.s	"	"
F10	"	"	0.6ml	q.s	"	"
F11	"	"	PEG 400 (0.6ml)	q.s	"	"
F12	"	"	PG (0.3ml) + Glycerol (0.3ml)	q.s	"	"
F13	"	"	PG (0.3ml) + PEG 400 (0.3ml)	q.s	"	"
F14	"	"	Glycerol (0.3ml) + PEG 400 (0.3ml)	q.s	"	"
F15	150mg	"	PG (0.2ml) + glycerol (0.2ml) + PEG 400 (0.2ml)	q.s	"	"
F16	150mg	HPMC E-15	Glycerol (0.3ml) + PEG 400 (0.3ml)	q.s	"	"
F17	150mg	HPMC E-15	PG (0.2ml) + Glycerol (0.2ml) + PEG 400 (0.2ml)	q.s	"	"

TABLE 2: FORMULATIONS WITH SURFACTANT

Formulation code	API	Polymer	Plasticizer 0.6ml	Surfactant	Water	Ethanol	Sweetening Agent
Fa1	150mg	Gelatin 150mg	Glycerol	Tween 80 (0.2ml)	q.s.	1ml	Mannitol (0.5ml)
Fa2	150mg	"	PEG 400 "	"	q.s.	"	"
Fa3	150mg	"	PG +glycerol "	"	q.s.	"	"
Fa4	150mg	"	PG +PEG 400 "	"	q.s.	"	"
Fa5	150mg	"	Glycerol + PEG 400	"	q.s.	"	"
Fa6	150mg	"	Glycerol + PG + PEG 400	"	q.s.	"	"
Fa7	150mg	HPMC E-15	Glycerol + PG + PEG 400	"	q.s.	"	"
Fa8	150mg	Gelatin 150mg	Glycerol	Tween 80 (0.4ml)	q.s.	"	"
Fa9	150mg	"	PEG 400 "	"	q.s.	"	"
Fa10	150mg	"	PG + glycerol "	"	q.s.	"	"
Fa11	150mg	"	PG + PEG 400 "	"	q.s.	"	"
Fa12	150mg	"	Glycerol + PEG 400	"	q.s.	"	"
Fa13	150mg	"	Propylene glycol + Glycerol + PEG 400"	"	q.s.	"	"
Fa14	150mg	HPMC E-15	Propylene glycol + Glycerol + PEG 400"	"	q.s.	"	"

Evaluation of Oral Thin Films:

1. **Thickness** [8]**:** Thickness of the films was measured at five points using micrometer to ensure the uniformity of film thickness. The mean thickness is calculated, the patches having thickness variation greater than 5% were excluded from analysis.

2. **Folding endurance** [8]**:** Folding endurance of film was determined by repeatedly folding the films of uniform cross sectional area (4*4 cm^2) until it breaks

3. **Swelling index:** Swelling index is performed to analyse the swelling of the film due to polymer (Gelatin and HPMC E-15).

4. **Drug content:** Drug content is determined by taking the film of 4cm^2 and dissolved in 100ml of phosphate buffer of 6.8pH. Then the solution is suitably diluted and the absorbance was recorded at 259nm.

5. **Surface pH:** The surface pH of the film was determined by using pH meter. OTF was slightly wet with the help of water. The pH was measured by bringing electrode in contact with the surface of the film. It is necessary to maintain the pH of the film, as an acidic or alkaline pH may cause irritation to the oral mucosa; it was determined to keep the surface pH as close as to neutral as possible.

6. ***In vitro*** **Disintegration time** [9, 10]: There are two simple methods in first method; one drop of dissolution medium was dropped from a 10-ml pipette onto the tightly clamped film. The time taken for the water to make a hole through the film was measured as disintegration time (DT). In the second method, 2 ml of water was placed in a petri plate with a film on the surface of water; the time taken for the disintegration of the film was measured. This test was done in triplicates and the average value was taken as disintegration time.

7. ***In-vitro*** **Dissolution Studies** [11]**:** *In-vitro* dissolution test was carried out in USP II paddle dissolution apparatus with 900ml of phosphate buffer as dissolution media. Temperature was maintained at 37±0.5^oC and set to a 100rpm.A film of 4cm^2 was cut and stick to the basket side wall.

5ml aliquots of samples was taken for every 30sec and followed by replacement of 5ml fresh phosphate buffer. The withdrawn samples were analysed spectrophotometrically at a wavelength of 259nm.

8. **Dissolution rate by Conductometry [12]:** Dissolution rate can also determined by measuring the conductivity. A beaker with 300ml of water was taken and determined the conductivity of the water to establish the background value. Arrange the conductivity probe, impeller and maintain temperature at 37±0.5°C. After adhering film to the beaker set the stirrer to 100rpm. Conductivity was measured for every 15 sec until the conductivity remains constant.

RESULTS AND DISCUSSIONS:

Evaluation Parameters:

1. **Thickness:** The mean thickness of the oral thin films was found to be in the range 0.087mm-0.098mm

2. **Folding Endurance**: The folding endurance of the oral thin films was found to be in the range 35-180. The films of formulations F8, F12, F14, F15,F16, F17, Fa3, Fa5, Fa6, Fa7, Fa10, Fa12, Fa13,Fa14 shows better plasticity. The remaining formulations are found to be highly brittle.

3. **Swelling Index:** Swelling index of the oral thin films was found to be in the range 93-157. Polymer of gelatin and HPMC E15 of weight 150mg showed better swelling property.

4. **Drug content:** The drug content of the oral strip of 4cm^2 was determined and it varies with the range of 97±0.0 to 99.54%.The drug content was found to be high in F14.As per USP, the drug content was found to be in range of 85-115%.

5. **Surface pH:** The surface pH of the drug was found to be 6.8- 7.4

6. ***In-vitro* Disintegration test:** Formulation containing surfactant showed better disintegration time.Fa6, Fa7, Fa8, Fa13, Fa14 shows better disintegration compared to F8, F12, F14, F15, F16, F17, Fa3, Fa5, Fa10 and Fa12.

7. ***In vitro* dissolution studies**: Formulation containing Tween 80 showed maximum drug release within 120 sec the release was found to be 98.8% Fa14, 96.4% Fa7, 94.8% Fa13, 90.8% Fa6 from **Table 4**. The release of Fa7 is less than Fa14 this can be attributed due to less concentration of surfactant. Fa13 shows less percentage release than Fa14 and Fa7 this can be attributed due to the formation of high viscous solution of gelatin which retards the drug release.

   Fa6 shows still lesser due to less surfactant concentration. The formulation without surfactant shows the following order of release F17 (89.2%)> F15 (87.6%) > F13 (85.9%). The other formulation released almost appropriately same amount of drug. The least percentage drug release was found to be F7.

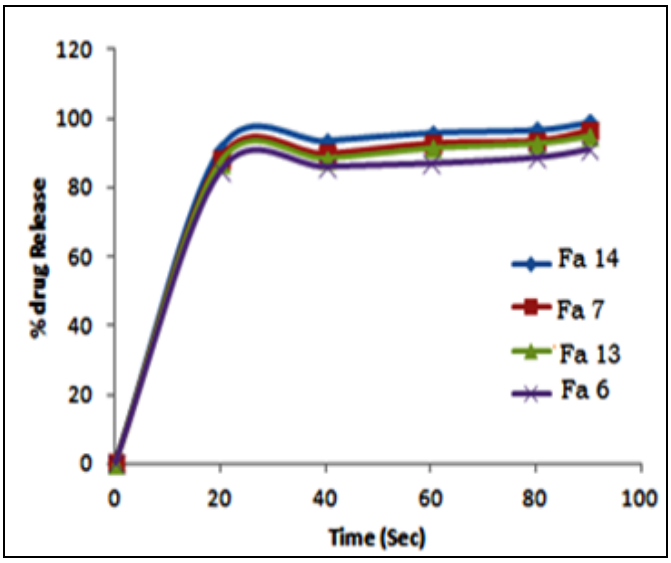

FIG. 3: TIME VS PERCENTAGE DRUG RELEASE OF DIPHENHYDRAMINE HCl IN PBS 6.8pH

Dissolution rate by Conductivity method: Conductivity is determined ionisable components. The film consists of Diphenhydramine HCl which is ionisable. Based on the release of the drug conductivity (µsimen/min) alters.

TABLE 4: THE FOLLOWING TABLE SHOWS THE PROPERTIES OF THE SUCCESSFUL FORMULATIONS:

Formulation code	Folding Endurance	Swelling Index	Disintegration Time	Conductance	% Drug Release
F17	120	116	35sec	48.6	87.2
F15	135	127	40sec	45.2	85.5
F13	180	127	55sec	39.5	83
Fa6	95	108	32sec	50.78	90.8
Fa7	124	147	27sec	54.4	96.4
Fa13	87	157	29sec	53.33	94.8
Fa14	93	149	25sec	56.32	98.8

CONCLUSION: Diphenhydramine Hydrochloride oral thin films were successfully prepared by solvent casting method using the following polymers: Gelatin, HPMC E15. 1:1 ratio of drug and polymer ratio was optimized. The films prepared by using Tween 80 which was used as solubilizing agent has more percentage drug release. Among all formulations, Films prepared using HPMC E15 with Tween 80 showed best results.OTF prepared by using HPME15, Platicizers (Glycerol, Propylene Glycol, PEG 400) and solubilizing agent Tween 80 would be promising oral delivery systems for Diphenhydramine Hydrochloride.

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