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PREPARATION AND EVALUATION OF TASTE MASKING ORAL DISINTEGRATING FILMS OF DICLOFENAC POTASSIUM USING SOLVENT CASTING METHOD.

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Abstract:

This research was carried out with the prime objective of taste masking oral disintegrating films of the drug that has undesirable taste like diclofenac potassium which was to enhance agreement among the ageing population, the new born and non compliant patient which facilitates the ease of its passage. The reason of this study was carried out to understand film forming properties of various ingredients like HPMC, Pullulan and polyvinyl alcohol polyethylene glycol based polymers that were used in these experiments. The folding endurance test , the way it peels and its disintegration time (in vitro) of plasticizers that included propylene glycol, sorbitol, glycerin polyethylene glycol 400 was evaluated . The method that was used to prepare it here was solvent casting method. The non placebo films containing the drug that consisted of the polymers with its plasticizer showed the best possible film forming capacity having an accepting folding endurance and a good disintegration time of 22 seconds and greater than 95 % of drug release within 10 minutes of time that was better than the tablets that were marketed and immediate release which gave a value of almost 30.4 % at the end of 10 minutes time. The films that were prepared were in the range of 30 – 40 milligram. It was taste masked by a mixture called as sucralose and monoammonium glycerrhizinate giving the best sweetness profile. The stability studies carried out on these ODT films showed that these were stable atleast for 3 months when it was stored at 40°C and that was having 75 % Relative Humidity. This formulation that was prepared was effortless and simple having least cost whenever there is a need to deliver the medicine especially in cases like joint stiffness where immediate onset of action was quite necessary.

Keywords: *Oral Disintegrating Film, Monoammonium Glycerrhizinate, Folding endurance, Solvent Casting, Diclofenac Pottasium.*

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INTRODUCTION:

We have witnessed in the past one decade that there has been an aspiration for more patient friendly and more compliant dosage forms to patients that cause no kind of hindrance in its application. To which it has put an ever increasing demand of usage of new technologies yearly. Oral Disintegrating films have made a place for its self in The Oral drug delivery system market as a result of this demand. [1-3]
Advantages of OD films include:

- Easy to apply
- Cost of production is less
- More patient friendly
- Ease of production
- Painless dosage form

Disadvantages of OD films include:

- May peel off if no proper adhesion
- May cause skin irritation
- Temporary bitterness might persist

Diclofenac Potassium is another salt form of the drug Diclofenac Sodium belonging to the class of NSAID. It works by reducing substances in the body that create the sensation of pain and also cause inflammation. It is almost 100 % absorbed after oral administration. It has an half life of about 2 hours.[5] In pain conditions especially for the elderly bedridden and patients that do not cooperate they feel that swallowing of drugs to be difficult. [6]

The aim of the present research work was to create a taste masking OD film of Diclofenac Potassium that would disintegrate within 30 seconds. This will make it sweet and better accepting and improving patient compliance when it is used. The polymers used here included modified starch [7,8], HPMC (E-5) [9] Pullulan [10,11] also containing poly vinyl alcohol PEG based polymer (Kollicoat IR) [12] these were evaluated for how good they form a film by considering parameters like folding endurance , peelability and invitro disintegration of these films. The bitter taste of the drug Diclofenac Potassium was masked by using a mixture that contained sucralose and monoammonium glycerrhizinate that gave a better sweetness profile [14]. The preparation encompassed was easy simple and very economical that could have a great applicability and also something that gave faster In vitro dissolution rates when it was compared available immediate release tablets in the market.

Selection of Polymers for ODF:

Modified starch (25%), HPMC E-5 (5-15%) , Pullulan (2-5%), Kollicoat IR (2 – 15 %) were taken as evaluated substances that form films. As well as glycerine, PG, Soribitol and PEG 400 as the plasticizers those were used. The plasticizers were taken and it was dissolved in distilled water and followed by dissolving in polymer by removing air by sonication. It was cast on Teflon plates. Followed by its drying at 60°C.

The film was then taken and it was evaluated for its film forming ability, The folding endurance [15] The peelability, The thickness, Uniformity and its in vitro disintegration. The polymer that gave the best results for its smoothness, non tackiness, flexibility and that disintegrated quickly was selected for its drug loaded film.

Determination of the value of Bitterness of Diclofenac Potassium:

There was a panel of 6 members in the age group of 23 – 26 that were considered to be healthy volunteers from whom prior permission was taken as this study constituted placing the drug solution in the mouth for about 30 seconds and not swallowing it. And then removal from the mouth by spitting and rinsing with water. There was a series of solutions of Diclofenac Potassium that was in the concentration ranges of 10, 20, 30, 40 and 50µg / ml. With the usage of Phosphate buffer of pH 6.8. Then the volunteers were asked to sip and keep the drug solution of 10 ml in their mouth for 30 seconds and also to rate the taste on the scale from 0 to 4 (where 0 having no bitterness 1 having threshold bitterness 2 being bitter 3 having moderate bitterness and 4 having strong bitterness) between the alternative tests the mouth was rinsed with clean water. Based on the reports of the volunteers it was determined that Diclofenac Pottasium was bitter. Then again by trial and error method various drugs containing sucralose containing peppermint powder with and without monoammonium glycerrhizinate. That was taken to mask the bitter taste of Diclofenac Potassium and these ratings were shown in the table 1.

Table 1: Testing Parametes rating scale.

Aspects	Rating Index
After Tasting	1 – No taste 2 – Slight Taste 3 – Extreme Taste
Flavour Magnitude	1 – Not Stong 2- Moderate 3 – Strong 4 – Very Stong
Bitterness	1 – No bitterness 2 – bitterness present at the end 3 – bitter 4 – extremely bitter

Preparation of the films:

The Drug loaded films were incorporated using a technique called Solvent casting method [16] which was for a more optimized film that was made of each polymer. Diclofenac Potassium was incorporated into the film at a concentration of 5 mg per 4 cm^2 of the available film area. The amount of the drug was calculated and inferred by the total amount of the solution that is to be poured in order to obtain films that had the desired thickness when it was casted on the total surface are of the plate. The polymer was weighed and added to $3/4^{th}$ quantity of water by stirring it continuously and removing the entrapped air by sonication . Diclofenac Potassium along with the sweetner sucralose and monoammonium glycerrhizinate was dissolved in the water that was left also having peppermint powder by stirring continuously. The two solutions were mixed to form a further homogenous solution that was also obtained by sonication. It was casted on the Teflon plates and dried completely at 60°C. It was then peeled off from the container and then taken to an air tight container (dessicator) under less humidity conditions until it was required for other evaluation tests.

Evaluation of the films containing the Drug:

The prime requisite which was the organoleptic properties of the drug loaded film was evaluated. A vernier calipers was taken and used to measure the thickness of each film formed at five different locations which included the Center and the four corners. This data was taken and it was shown as a mean±SD of triplicated films. The films were cut into dimensions of 2×2 cm of strips that were in square shape. By exposing these films to relative humidity of 75% and a temperature of (25±2°C) for a time period of about one week[17]. Percentage increase in weight was taken as the parameter to determine the reuptake of moisture by the films. Tack is the property by which the film adheres to where it is applied to which it comes in contact with. The film was checked if it is Tacky or Non tacky by placing it between the fingers in this way tackiness evaluation [18] was carried out. The property of softening upon storage was checked by placing these films in the dessicator for a time period of 2 days. The evaluation tests for softening and integrity was carried out this way.

The folding endurance test was determined by continuously folding the same film at the same place till the film breaks. The folding endurance value was calculated by taking the number of times the folding was done. The In vitro dissolution test was performed by taking the OD film and placed in glass petri plate containing 6 ml of water and the time required for the film to break was noted down. The usual disintegration time was in the range of 5 – 30 seconds [19]. Drug content determination was performed by UV Spectroscopy at 242 nm. It was performed by using Type 2 Dissolution Apparatus at 37°C stirring at 50 rpm in 900ml of beaker containing 0.1 N hydrocholricacid this test was compared to the dissolution of Cataflam 5 mg under the same dissolution conditions. 5 ml o f the dissolution fluid was colleted and was checked by filtering the concentration of Diclofenac Pottasium at a time intervals of 1, 2, 5, 10, 15 and 30 time intervals of time . these results were then presented as an average

Stability Studies

Accelerated stability conditions were used to check the stability conditions which were (40±2°/75±5% RH) by keeping it in a stability chamber for three months which was according to the International Conference on Harmonization (ICH) guidelines. The samples were evaluated for the physical strength and after 3 months and 1 month the in vitro drug dissolution was carried out.

RESULTS AND DISCUSSION:

This study was carried out to have knowledge of polymers such as Modified starch, Pullulan HPMC E-5 and Kollicoat IR if they were able to form films that were required. The primary requisite was to develop a film that had good organo leptic polymers and also that had various concentrations. Organoleptic characteristics including appearance peel ability and non tackiness also having an in vitro dissolution time of less than 30 seconds. In our studies 30 seconds was taken as the criteria.

By observing the results given in Table 2 and Table 3 Modified starch at concentration of 10 % w/w showed no film formation also at a concentration of 25% w/w it showed a good peel ability to give it a more flexible characteristic of the film and also increase the wetting property Polysorbate 80 were added. At 2 % w/w it showed that the films formed were brittle and had low folding endurance and at 4% w/w it showed good folding endurance and better film forming ability. Polysorbate 80 concentration was fixed at 2 % w/w of the polymer that was used it was found that when a small amount of soya lecithin was added (0.8 % and 0.1% polysorbate 80 was added) it gave the desired result of wetting and better dissolution. Also it was observed that no film softening was observed upon storage. Hence MF9 was selected for drug loading

Table 2: Physico- Chemical properties of Modified Starch Polymer Films

Formulation name and Number	MF1	MF2	MF3	MF4	MF5
Film forming ability	Poor	Poor	Good	Good	Good
Peeling ability	Non Peel able	Non Peel able	Peel able	Brittle during peeling	Non Peel able
Appearance	Transparent	Transparent	Transparent	Transparent	Transparent
Tackiness	Non Tacky	Non Tacky	Non Tacky	Tacky	Non Tacky
Folding Endurance number	-	5	27	8	11
In Vitro Disintegration Time (seconds)	Non Disintegrating	Non Disintegrating	Non Disintegrating	38	31
Film Softening of the Polymer	Softening	Softening	Softening	Non Softening	Non Softening
Selected	No	No	No	No	No

Table 3: Physico Chemical properties of Modified Starch (Continued)

Formulation name and Number	MF6	MF7	MF8	MF9
Film forming ability	Good	Good	Good	Very Good
Peeling ability	Peel able	Peel able	Peel able	Peel able
Appearance	Transparent	Transparent	Transparent	Transparent
Tackiness	Tacky	Non Tacky	Slightly Tacky	Non Tacky
Folding Endurance number	28	21	33	31
In Vitro Disintegration Time (seconds)	36	27	21	18
Film Softening of the Polymer	Non Softening	Non Softening	Non Softening	Non Softening
Selected	No	No	No	No

By observing the test results for Pullulan in Table 4 it formed a good peel able film at a 2 % w/w and a 5%w/w concentration having an in vitro disintegration test less than 30 seconds. Thus Pullulan with lower concentration was selected for further trials. The properties of different plasticizers were also conducted. Sorbitol incorporated in the film showed good folding endurance amd no film softening effect. Hence 5 % w/w of Pullulan film of the batch was selected having a formulation number of PF5 containing 5 % Pullulan for loading.

After observing the results given in Table 5 it was noticed that HPMC E- 5 formed a good peel able film at 5 % w/w. The effect of various plasticiziers used was studied at concentrations of 0.1% and 0.7 % polysorbate. PG was selected as it was found to give a lesser Dissolution time. 1% PG along with 5 to 7 % of HPMC was carried out with increasing thickness and In vir dissolution time was at 10 seconds. Hence HF5 was selected as drug loading.

Table 4: Physico Chemical properties of Pullulan Polymer films produced.

Formulation name and Number	PF1	PF2	PF3	PF4	PF5
Film forming ability	Good	Good	Good	Good	Very Good
Peeling ability	Non peel able	Peel able	Peel able	Brittle During Peeling	Easily Peel able
Appearance	Transparent	Transparent	Transparent	Opaque	Transparent
Tackiness	Non Tacky	Tacky	Non Tacky	Non Tacky	Non Tacky
Folding Endurance number	20	35	29	32	39
In Vitro Disintegration Time (seconds)	25	16	20	18	15
Film Softening of the Polymer	Softening	Non Softening	Softening	Softening	Non Softening
Selected	No	No	No	No	Yes

Table 5: Physico Chemical properties of HPMC E5 Polymer films produced.

Formulation name and Number	HF1	HF2	HF3	HF4	HF5	HF6
Film forming ability	Good	Good	Good	Good	Very Good	Poor
Peeling ability	Peel able	Peel able	Easily Peel able	Peel able	Easily Peel able	Peel able
Appearance	Transparent	Opaque	Transparent	Transparent	Transparent	Transparent
Tackiness	Non Tacky	Non Tacky	Non Tacky	Non Tacky	Non Tacky	Tacky
Folding Endurance number	20	22	35	23	40	-
In Vitro Disintegration Time (seconds)	20	15	10	15	10	-
Film Softening of the Polymer	Softening	Softening	Non Softening	Softening	Non Softening	Softening
Selected	No	No	Yes	No	Yes	No

By observing the results given in Table 6 it was known that Kallicoat IR did not form any film at a concentration if 2 % it formed good peel able film at 5% and 10 %. Thus 10 % w/w was finalized. Polysorbate 80 was incorporated as a wetting agent. The formulation KF3 showed all desired properties and hence it was incorporated into the drug loading.

From all the volunteers, Most of them found that 20 µg / ml was the threshold value of bitterness of Diclofenac Potassium. This indicated that the drug is bitter and needed efficient taste masking methods before it could be formulated into OD Films. In order for patients to approve of it and for it to be used as an OD Films this factor becomes essential. This product was successfully taste masked using sucralose which acted as a sweetner Peppermint acted as a flavouring agent and monoammonium glycerrhizinate acted as the flavor enhancer. Sucralose gives that intial burst of sweetness but it loses it after a while but when it is given along with monoammonium glycerrhizinate the sweetness profile of this lasts longer. From all the trial and errors the batch F3 was selected that had the mixture in combination of 2 mg of sucralose, 2mg of pepper mint powder and 0.2 mg of monoammonium glycerrhizinate.

The incorporation of these drugs and the drug loading was carried out and it gave successful results (Table 8) showing no change in characteristics that were desired. The characterization of Diclofenac Potassium and its results and evaluation was given in Table 9. Films having the formula LODF01 were considered to be non tacky being smooth and being transparent also having a thickness of 0.2 mm. It showed the best dissolution time within 30 seconds. This showed that drug loading did not affect any of the properties of the modified starch polymer film. When compared to the Pullulan film it was non tacky being transparent and disintegrating within 15 seconds. HPMC E5 polumer showed disintegration within 10 seconds the film obtained from this was non tacky and showed a good folding endurance of 40. Drug loaded with Kollicoat IR was also non tacky in nature, it was flexible being transparent and having a folding endurance 37. It is evident that Kollicoat IR consists of 75 % Polyvinyl alcohol and also consist of 25 % of PG Thus there was no actual need for an additional polymer.

Table 6: Physico Mechanical properties of kollicoat polymers produced

Formulation name and Number	KF1	KF2	KF3	KF4
Film forming ability	Poor	Good	Very Good	Poor
Peeling ability	Non Peel able	Peel able	Easily Peel able	Non Peel able
Appearance	-	Transparent	Transparent	-
Tackiness	-	Non Tacky	Slight Tacky	-
Folding Endurance number	-	30	37	-
In Vitro Disintegration Time (seconds)	-	29	21	-
Film Softening of the Polymer	Softening	Softening	Non Softening	Softening
Selected	No	No	Yes	No

Table 7: These were the test scores given by the Volunteers.

Formulation Number	F1	F2	F3
After Tasting	3	2	1
Flavour magnitude	1	1	2
Bitterness	3	3	1

Table 8: Shows the concentration of Diclofenac Potassium in W/W

Contents	LODF01 Modified Starch	LODF02 Pullulan	LODF03 HPMC E – 5	LODF04 Kollicoat IR
Modified Starch	25	-	-	-
Pullulan	-	5	-	-
HPMC E- 5	-	-	7	-
Kollicoat IR	-	-	-	10
Polysorbate 80	0.1	0.1	0.1	0.1
Soya Lecithin	0.8	-	-	-
Sorbitol	4	0.5	-	-
Sucralose	1	1	1	1
PEG	-	-	1	-
Monoammonium Glycerrhizinate	0.1	0.1	0.1	0.1
Peppermint powder	0.8	0.8	0.8	0.8
Distilled Water	q.s.	q.s.	q.s.	q.s.

Table 9: The Physico Chemical properties of Diclofenac Potassium OD Film.

Test Parameters	LODF01 Modified Starch	LODF02 Pullulan	LODF03 HPMC E- 5	LODF04 Kollicoat IR
Appearance	Transparent and Smooth	Transparent and Smooth	Transparent and Smooth	Transparent and Smooth
Taste	Minty	Minty	Minty & Sweet	Sweet
Tack test	Non Tacky	Non Tacky	Non Tacky	Non Tacky
Thickness in mm	0.2	0.2	0.2	0.2
In Vitro Disintegration time in seconds	18	15	10	21
Folding Endurance	31	40	40	37
% Drug Content	98.29	101.36	99.2	102
Film Softening	No Film Softening	No Film Softening	No Film Softening	No Film Softening
% Moisture uptake	0.4	0.66	0.81	0.62
Acceptable or Not	Acceptable	Acceptable	Acceptable	Acceptable

When compared to the marketed formulation which showed immediate release the Dissolution time profile of OD film showed greater than 95 % in 10 minutes whereas the marketed formulation Cataflam showed 30.4% dissolution in 10 minutes of time and 100 % of dissolution in about 28 minutes of time. The accelerated stability test conditions showed that when placed at conditions (40±2°/75±5% RH)for 3 months it showed no change in its appearance thickness folding endurance or In vitro disintegration time and In vitro Dissolution time.

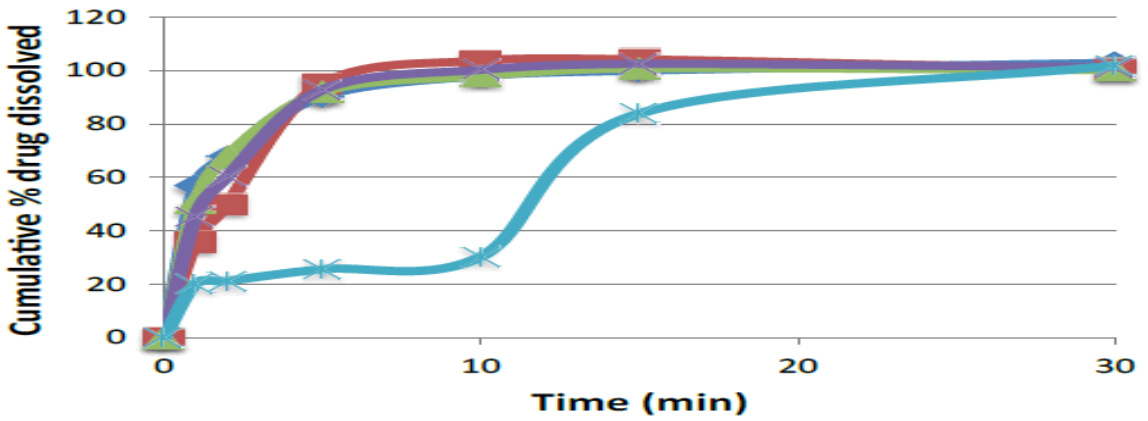

Fig. 1: *In vitro* drug dissolution profile of ODF vs. immediate release marketed tablet
—◆— LODF01; —■— LODF02; —▲— LODF03; —×— LODF04; —*— IR marketed tablets

Table 10: Stability of Modified Starch

Conditions	(% RH)	Initial day	30th Day	90th Day
Appearance	40/ 75 25/60	Transparent Transparent	Transparent Transparent	Transparent Transparent
Thickness in mm	40/ 75 25/60	0.2 mm 0.2 mm	0.2 mm 0.2 mm	0.2 mm 0.2 mm
Folding Endurance	40/ 75 25/60	31 32	30 29	32 30
% Moisture Uptake	40/ 75 25/60	0.4 0.52	0.4 0.42	0.42 0.48
In Vitro Dissolution Time	40/ 75 25/60	18 20	20 22	18 20
Assay %	40/ 75 25/60	98 99	98.5 100	101.5 100.2

Table 11: Stability Studies of Pullulan ODF

Conditions	(% RH)	Initial day	30th Day	90th Day
Appearance	40/ 75 25/60	Transparent Transparent	Transparent Transparent	Transparent Transparent
Thickness in mm	40/ 75 25/60	0.2 mm 0.2 mm	0.2 mm 0.2 mm	0.2 mm 0.2 mm
Folding Endurance	40/ 75 25/60	40 35	38 33	36 30
% Moisture Uptake	40/ 75 25/60	0.6 0.5	0.5 0.5	0.58 0.48
In Vitro Dissolution Time	40/ 75 25/60	20 20	18 22	20 20
Assay %	40/ 75 25/60	102 101	102.2 101.5	102 100

Table 12: Stability Data of HPMC E- 5

Conditions	(% RH)	Initial day	30th Day	90th Day
Appearance	40/ 75 25/60	Transparent Transparent	Transparent Transparent	Transparent Transparent
Thickness in mm	40/ 75 25/60	0.2 mm 0.2 mm	0.2 mm 0.2 mm	0.2 mm 0.2 mm
Folding Endurance	40/ 75 25/60	40 35	38 36	36 30
% Moisture Uptake	40/ 75 25/60	0.8 0.5	0.7 0.6	0.8 0.6
In Vitro Dissolution Time	40/ 75 25/60	20 25	22 20	21 24
Assay %	40/ 75 25/60	99 98	101 101.5	101.5 100.2

Table 13: Stability Studies of Kollicoat OD Film

Conditions	(% RH)	Initial day	30th Day	90th Day
Appearance	40/ 75 25/60	Transparent Transparent	Transparent Transparent	Transparent Transparent
Thickness in mm	40/ 75 25/60	0.2 mm 0.2 mm	0.2 mm 0.2 mm	0.2 mm 0.2 mm
Folding Endurance	40/ 75 25/60	37 32	38 31	36 32
% Moisture Uptake	40/ 75 25/60	0.6 0.58	0.62 0.58	0.6 0.65
In Vitro Dissolution Time	40/ 75 25/60	20 22	26 24	23 21
Assay %	40/ 75 25/60	101 99.5	102 101.2	102 100.8

CONCLUSION:

Modified Starch (25%), Pullulan (5%) Kollicoat IR (5%) and HPMC E- 5 (7 %) of Diclofenac Pottasium formed properties which were peel able, transparent, flexible and fast dissolving which weighed around 50 mg and showed disintegration time within 30 seconds. This formulation showed faster disintegration and dissolution time profiles when compared to the normal immediate marketed tablets. This had taste masking abilities. They may promise to be more efficacious. In case of non cooperative patients these offer a very potential use and an alternative solution.

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