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FORMULATION AND EVALUATION OF ORODISPERSIBLE FILMS OF ACECLOFENAC

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ABSTRACT

The present work was aimed to formulate Oro Dispersible Films (ODF) of Aceclofenac with improved solubility and patient compliance. ODFs or fast dissolving films are the new dosage formulation which are becoming most preferred drug delivery systems. ODFs have advantages over other formulations like improved solubility of poorly soluble drugs, enhanced patient compliance, instant release of drug, avoiding hepatic first pass effect, etc. Aceclofenac is one of the poorly water-soluble drug which is used as NSAID having analgesic and anti-inflammatory actions. Hence Aceclofenac was used in the present study to enhance the solubility by formulating in the form of ODF. The films were prepared by Solvent Casting method by dissolving Aceclofenac and other excipients like Hydroxy Propyl Methyl Cellulose (HPMC), β-Cyclodextrin, Propylene glycol, CrossCormellose Sodium (CCS), Sodium Saccharin. The low solubility of Aceclofenac was a greatest challenge which was overcame by incorporating β-cyclodextrin. The formulated films of Aceclofenac were evaluated in terms of Thickness, Folding endurance, Surface PH, Weight variation, Drug content, Disintrgration time, FTIR analysis, and Dissolution studies. Among all the formulations, F4 formulation was found to be optimized ODF as it has lower disintegration time and high dissolution rate due to high concentration of CCS. The other formulations showed moderate results. FTIR studies indicates that there is no interaction between drug and excipients. The addition of β-Cyclodextrin to F3 and F4 formulation showed improved solubility as compared to F1 and F2 formulations.

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INTRODUCTION

Oral route of administration of drugs is most preferred way, as it has many advantages like ease of administration, offer great patient compliance and non-invasive [1]. The orodispersible films are also known as fast dissolving films or oral thin films which rapidly release the drug when placed on the tongue. Oral mucosa is highly vascularized which facilitates drug absortion into systemic circulation, a novel approach to formulate drugs in the form of thin oral disintegrating films for drugs having low solubility [2]. ODFs are the flat thin films administered orally for delivery of drug systemically for OTC medications [3]. ODFs have become most preferred oral dosage form as they provide greater surface area which results faster wetting and disintegrating, which improves acceptance in patients who have problems like chewing, swallowing or ingesting the drug [4]. Solubility is the major parameter for drug development, about 35-45% of drugs are poorly water soluble and results in high disintegration and low bioavailability which is a major concern in drug development. BCS class II and IV have drugs with low solubility and high permeability. The drugs include Aceclofenac, Ezetimib, Phenytoin, etc. The solubility of such poorly water drugs can be enhanced by formulating in the form of orodispersible films. The various types of orodispersible formulations are orodispersible films, orodispersible tablets, orodispersible granules, oral lyophilisates [5]. Bitter taste of drugs is another major problem which can be overcome by oral thin films by preventing the interactions between the drug and taste receptors by molecular complexation with cyclodextrins [6]. Therapeutic proteins like vaccines, antibodies, enzymes, hormones, etc are sensitive, so easily degraded in acidic conditions of GIT and have poor absorption from GIT, this can be overcome by formulating proteins in the form of ODFs [7]. ODFs dissolve rapidly within seconds on contact with saliva without the need of water, thereby improving the compliance for pediatric and geriatric patients [8]. ODFs provide improved safety by reducing the risk of suffocation or chocking due to physical obstruction during oral administration of conventional solid dosage forms [9]. A wide range of drugs are formulated as ODFs for their pharmacological actions, examples include expectorants, anti-tussives, anti-asthmatics, anti-epileptics, etc [10].

Apart from having various advantages, ODFs also have limitations like- high ODF stickiness results in improper handling of film; ODFs may not be the choice of dosage form in case of patients with dry mouth syndrome (impaired saliva production) [11]. The other major challenges for ODFs include- necessity of taste masking for APIs having unpleasant taste; difficult to maintain uniformity of dosage; APIs which are unstable at buccal PH cannot be formulated as ODFs; the drugs which causes irritation of buccal mucosa cannot be administered; large doses of APIs cannot be incorporated [12]

Orodispersible films are formulated using water soluble polymers like Hydroxy Propyl Methyl Cellulose (HPMC), Pullulan, Hydroxy Propyl Cellulose (HPC), Maltodextrin [13]. ODFs can be formulated by various methods like Solvent casting method, Hot melt extrusion, Semisolid casting method, Rolling method etc [14].

Aceclofenac belongs to the group of Non-steroidal anti-inflammatory drugs (NSAIDs) which is a Phenylaceticacid derivative having anti-inflammatory and analgesic activities [15]. It is a white crystalline solid, practically insoluble in water, freely soluble in acetone and soluble in ethanol (96%) [16]. It mainly acts by inhibiting CycloOxygenase (COX), thereby reducing prostaglandin production. Aceclofenac is used in the treatment of Rheumatoid arthritis, Osteoarthritis and other joint diseases [17]. Aceclofenac has other therapeutic uses like- used in the treatment of Dysmenorrhea, Dental pain management, Pharyngomygdalitis, Low back pain, Peridural fibrosis, etc. Aceclofenac has adverse effects like gastric ulcers and gastric mucosal irritation [18].

In the present research work, Aceclofenac (NSAID) is used to formulate as ODF. The main objective of present work is to improve the solubility of poorly soluble Aceclofenac by formulating in the form of orodispersible film. All the formulated Aceclofenac ODFs were evaluated by various tests and the optimized formulation was developed. The addition of β-cyclodextrin has improved the solubility of F3 and F4 formulations compared to F1 F2.

MATERIALS AND METHODS

MATERIALS:

Aceclofenac was obtained from Hetero Pharmaceutical Company, Hyderabad, Telangana. CrossCarmellose Sodium, Sodium Saccharin, β-Cyclodextrin, Propylene Glycol, Hydroxy Propyl Methyl Cellulose (HPMC) were obtained from SD Fine- Chem Limited.

METHODS:

Estimation of Aceclofenac

Aceclofenac was estimated using Spectrophotometric method at 273 nm in PH 6.8 Phosphate buffer.

Construction of calibration curve

Accurately weighed amount of Aceclofenac was dissolved in methanol (3-4 ml) to prepare 1 mg/ml solution. From this solution, dilutions were made with PH 6.8 phosphate buffer to prepare a series of standard solutions containing 2,4,6,8, and 10 µg/ml of Aceclofenac. The solutions were analysed in the region 200-400 nm using UV spectrophotometer (LAB INDIA UV) and the absorbance was measured at 273 nm using PH 6.8 Phosphate buffer as blank. The calibration curve of Aceclofenac was developed, shown in the figure 1.

Table 1: Calibration table.

S.No	Concentration (µg/ml)	Absorbance
1	0	0
2	2	0.017
3	4	0.106
4	6	0.121
5	8	0.20
6	10	0.261

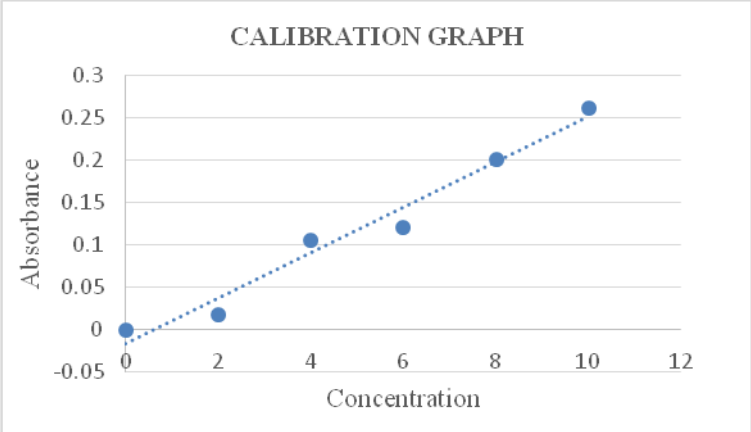

Figure 1: Calibration curve of Aceclofenac (µg/ml).

Method of preparation of Aceclofenac Orodispersible Films [19]

The ODFs were prepared by Solvent Casting method using various excipients like HPMC (film forming agent), CrossCarmellose Sodium (super disintegrant), Sodium saccharin (sweetening agent), Propylene glycol (plasticizer), β-Cyclodextrin (complexing agent) with different concentrations of CCS. HPMC was dissolved in water by using magnetic stirrer. Sodium saccharin, CCS, Propylene glycol, β-cyclodextrin were added to polymer solution of HPMC and stirred on a magnetic stirrer. Accurately weighed quantity of Aceclofenac was added to above solution and stirred by using a magnetic stirrer. After completion of stirring, the solution left for 5 minutes to remove air bubbles. This solution was poured uniformly into a petri dish and dried in hot air oven at 50^0c for 10 hours. The films were removed carefully and cut into required size (2×2 cm^2). The samples were stored for further evaluation.

Table 2: Formulation ingredients.

Excipients	Formulation			
	F1	F2	F3	F4
Aceclofenac (mg)	100	100	100	100
HPMC (mg)	400	400	400	400
CCS (mg)	5	10	20	25
Propylene glycol (ml)	0.1	0.1	0.1	0.1
Sodium saccharin (mg)	10	10	10	10
B-cyclodextrin (mg)	-	-	100	100
Water (ml)	10	10	10	10

EVALUATION OF ORODISPERSIBLE FILMS OF ACECLOFENAC

Morphological evaluation

To determine the morphological characteristics, the following properties of ODFs were studied- colour, transparency and stickiness of films by visual inspection

Thickness [20].

Thickness of film can be measured by using micrometer screwgauge. The thickness of all the films (2×2 cm^2) was measured at 5 different locations by using screwgauge.

Folding Endurance

Folding endurance is measured to determine mechanical properties of a film by repeatedly folding a film (2×2 cm^2) at same point until it breaks. The folding endurance value indicates the number of folds of a film without breaking. Higher the folding endurance value greater the mechanical strength of film.

Surface PH [21]

Surface PH of the film was measured by using PH indicator paper. The PH indicator paper was placed on the surface of the film and the PH was noted.

Weight Variation [22]

Weight variation was calculated by taking individual weight of the film (2×2 cm^2) three times and calculated the average weight of each film.

Drug Content

Drug content test is performed to determine the uniform content of drug in each film. 5 mg of film was weighed and dissolved in 20 ml of methanol. 0.1 ml of above solution was diluted with 10 ml of methanol and absorbance was measured at 273 nm using UV spectrophotometer (LAB INDIA UV).

Disintegration [23]

The film (2×2 cm^2) was placed in a petri dish and 7.5 ml of PH 6.8 phosphate buffer was added and petri dish was shaken constantly until the film disintegrates. The time taken to disintegration was noted.

Dissolution Studies [24]

In-vitro dissolution studies for ODFs of Aceclofenac was performed by using IP-1 dissolution test apparatus (ELECTROLAB) at 37 ± 0.5^0 c and a rotation speed of 100 rpm. The film (2×2 cm^2) was sticked on to a glass slide and placed in the basket containing 900 ml of phosphate buffer of pH 6.8. Specified aliquots were withdrawn for 5 minutes interval for a period of 30 minutes and each time replaced with equal volume of fresh buffer. The amount of drug released was analysed by using UV spectrophotometer (LAB INDIA UV) at 273 nm.

Fourier Transform Infrared Spectroscopy (FTIR) Studies [25]

Atentuated Total Reflectance- Fourier Transform Infrared Spectroscopy (BRUKER) was used to determine the interaction between the Aceclofenac (API) and the excipients. The drug, excipients and the final formulation were individually placed on a crystal, pressed and spectra were recorded. The background was obtained using a freshly cleaned crystal. The analysis was done in the frequency range between 4000 cm^{-1} and 400 cm^{-1}.

RESULTS AND DISCUSSIONS

Morphological Evaluation

Table 3: Morphological characteristics of films.

Formulation	Colour	Transparency	Stickyness
F1	White	Opaque	Non-sticky
F2	White	Opaque	Non-sticky
F3	white	Opaque	Non-sticky
F4	white	opaque	Non-sticky

Thickness

The thickness of prepared Aceclofenac films (2×2 cm^2) was measured by using Screw Guage. The determination of this measurement was to know the suitable thickness of the film to be placed on the tongue without any uneasyness.

Folding Endurance

The folding endurance test was carried out to check the brittleness of the film and the ability of the film to withstand the mechanical stresses like processing, handling and packaging.

Surface PH

The surface PH of the film was measured to verify the PH of the film is neutral as that of buccal cavity, to avoid irritation and to enhance patient acceptance.

Weight Variation

Weight variation test is performed to ensure that each formulation has the accurate amount of drug.

Drug Content

Drug content test is performed to determine the amount of active drug present in 2×2 cm^2 film.

Table 4: Evaluation of fast dissolving Aceclofenac films.

Formula-tion	Thickness (mm)	Folding endurance	Surface PH	Weight variation	Drug content (%)
F1	0.5	101	6.69	0.112	97.5
F2	0.5	103	6.75	0.133	98.2
F3	0.5	101	6.79	0.104	98.9
F4	0.5	102	6.80	0.195	99.3

Disintegration Time

Disintegration time indicates the time taken for the dosage form to disintegrate in the gastric juices. The disintegration time of different formulations (F1,F2,F3 and F4) are listed in the table 5.

Table 5: Disintegration time profile of fast dissolving Aceclofenac films.

S.No	Formulation	Time (Seconds)
1	F1	102
2	F2	86
3	F3	68
4	F4	43

F4 formulation has the less disintegration time i.e 43 seconds, as it has high concentration of super disintegrant (4.5%).

Dissolution

Dissolution is carried out to determine percentage drug release from the formulation at various time intervals.

Table 6: Dissolution profile of Aceclofenac formulations.

S.No	Time	% Drug release			
		F1	F2	F3	F4
1	0	0	0	0	0
2	5	22.68	28.67	30.28	31.54
3	10	39.89	41.25	44.99	47.92
4	15	50.28	53.48	56.76	60.67
5	20	68.13	69.74	70.10	72.86
6	25	76.24	78.23	85.58	86.48
7	30	88.76	89.99	92.97	98.95

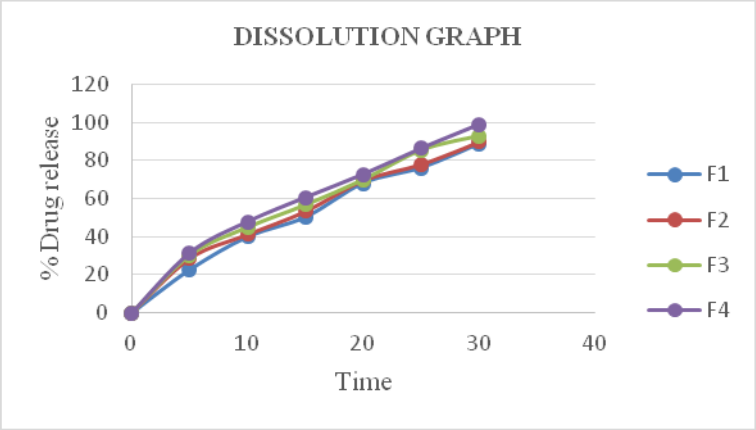

Figure 2: Dissolution profile of Aceclofenac formulations.

FTIR (Fourier Transform Infrared Spectroscopy)

FTIR analysis is performed to determine the interactions between drug and excipients.

FTIR spectrum of HPMC shown in the figure 3, The characteristic peaks were observed at 3566.66, 2903.12, 1456.76 and 1058.92 cm^{-1}, revealing the presence of Hydroxyl group (OH) stretching, C-H group, Vibration of hydroxyl group (OH) and C-O group stretching respectively.

FTIR spectrum of croscarmellose sodium shown in figure 4, the characteristic peaks were observed at 3674.57, 2958.47 and 1748.11 cm^{-1}, revealing the presence of hydroxyl group (OH) stretching, C-H group, C-O group stretching respectively.

FTIR spectrum of Sodium saccharin shown in figure 5, the characteristic peaks were observed such as C=O absorption at 1647.40 cm^{-1}, C-C benzene ring stretching at 1558.40 cm^{-1}, - SO_2 -N stretching at 1251.48 and 1145.93 cm^{-1}, Carbonyl bending were appeared at 971.14 and 746.09 cm^{-1}.

The FTIR spectrum of Propylene glycol shows C-H stretching at 1376.21, OH stretching at 3700-3100 cm^{-1}, broad band between 1100 and 900 cm^{-1} comes from the stretching vibrations of C-O in C-O-H bonds. Shown in figure 6.

The FTIR spectrum of β-cyclodextrin shows OH stretching at 3202.89 cm^{-1}, CH_2 stretching at 3090.55 cm^{-1}, C-C stretching at 1153.78 cm, bending vibrations at 1026.18 cm^{-1}. Shown in figure 7.

The FTIR spectrum of Aceclofenac showed characteristic bands at 3315.70 cm^{-1} (N-H stretching), 3133.56 cm^{-1} (O-H stretching), 1716.15 cm^{-1} (C=O stretching), CH_2 bending vibration at 1418.57 cm^{-1}. Shown in figure 8.

The FTIR spectrum of Aceclofenac optimized formulation bears the peaks of spectrum corresponding to the Aceclofenac peaks and other excipients with no significant shift in the major peaks, this indicates, there is no interactions between the drug and the excipients. All the peaks of Aceclofenac are prominant indicating the maintenance of drug identity and stability in the film. Shown in figure 9.

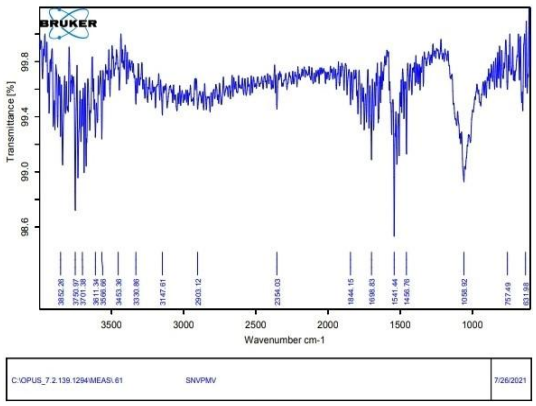

Figure 3: FTIR of Hydroxy Propyl Methyl Cellulose (HPMC).

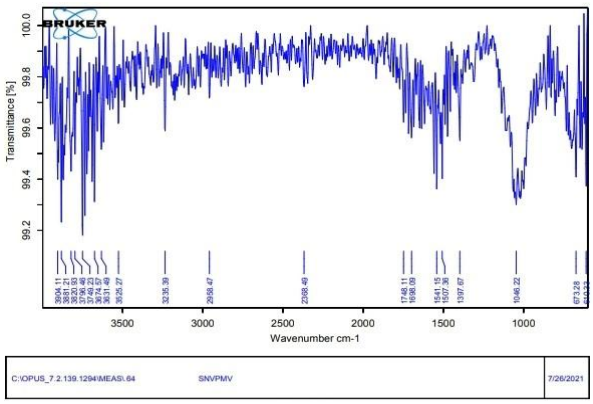

Figure 4: FTIR of Croscormellose Sodium.

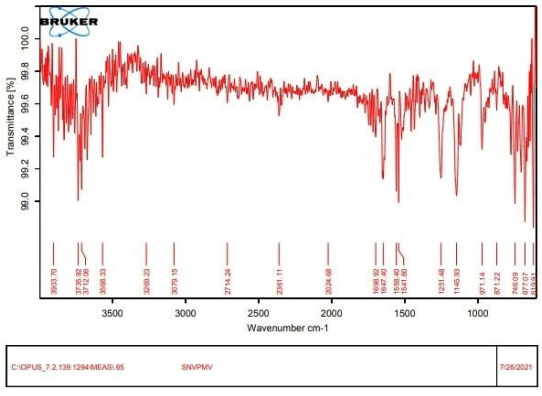

Figure 5: FTIR of Sodium Saccharin.

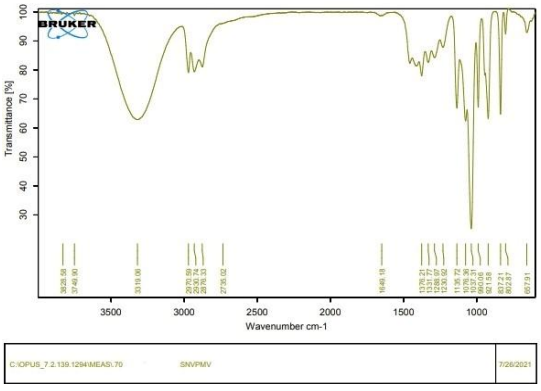

Figure 6: FTIR of Propylene Glycol.

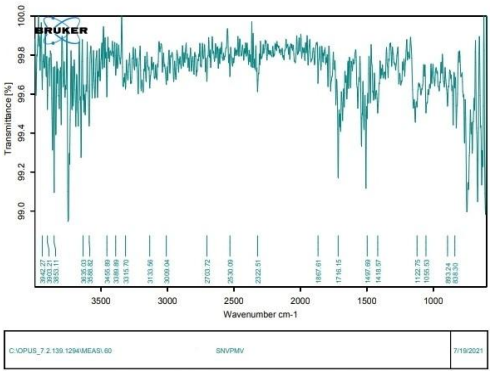

Figure 7: FTIR of β- Cyclodextrin.

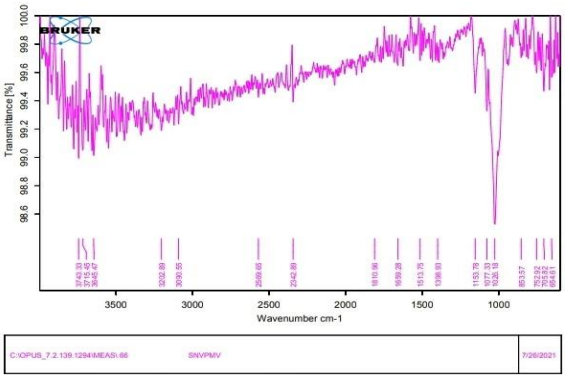

Figure 8: FTIR of Aceclofenac.

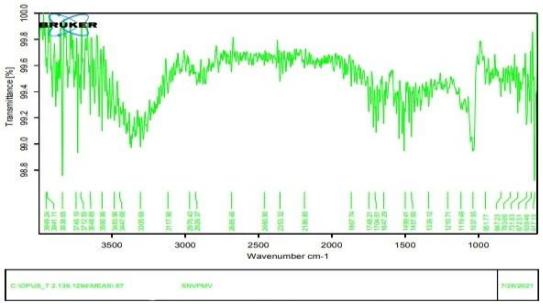

Figure 9: FTIR of Aceclofenac optimized formulation.

CONCLUSION

All the Aceclofenac ODFs were formulated by solvent casting method with different concentrations of CCS. Among all the formulations, F4 formulation found to be optimized formulation with lower disintegration time and highest dissolution rate as it has high concentration of CCS. F2 and F3 formulations have moderate disintegration and dissolution rates and F1 has the highest disintegration and low dissolution rates. FTIR studies shows no interactions between drug and the excipients. The other evaluation tests results of all the formulations showed profound results. The addition of β- cyclodextrin in F3 and F4 has improved the solubility of Aceclofenac compared to F1 and F2 formulations. The ODFs can be better and preferred dosage form for development of pharmaceutical products because of their wide range of advantages like patience acceptance, ease of administration, etc as compared to conventional dosage forms. Hence this drug delivery system has to be explored more for further development of new formulations of several drugs with poor solubility and other formulations like vaccines, anti-bodies, enzymes etc.

ABBREVIATIONS

ODF - Oro Dispersible Films
HPMC - Hydroxy Propyl Methyl Cellulose
HPC - Hydroxy Propyl Cellulose
CCS - Cross Carmellose Sodium
UV - Ultra Violet
FTIR - Fourier Transform Infrared Spectroscopy
OTC - Over The Counter
IP - Indian Pharmacopoeia
NSAIDs - Non- Steroidal Anti- Inflammatory Drugs

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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