International Journal of Current Advanced Research
ISSN: O: 2319-6475, ISSN: P: 2319-6505, Impact Factor: 6.614
Available Online at www.journalijcar.org
Volume 7; Issue 8(H); August 2018; Page No. 15110-15117
DOI: http://dx.doi.org/10.24327/ijcar.2018.14234.2757

Research Article

FORMULATION AND CHARACTERIZATION OF INDOMETHACIN CYCLODEXTRIN LOADED MOUTH DISSOLVING FILMS

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ARTICLE INFO

Article History:

Received 11th May, 2018
Received in revised form 7th June, 2018 Accepted 5th July, 2018
Published online 28th August, 2018

Key words:

Indomethacin, cyclodextrins, HPMC, PEG, MDF (mouth dissolving film), SLS, SSG.

ABSTRACT

The present investigation was undertaken in formulating mouth dissolving film(s) of the non-steroidal anti-inflammatory drug indomethacin. The main objective is to enhance the quick on set of action, convenience and compliance by the elderly and pediatric patients without the problem of swallowing and using water. Indomethacin belongs to BCS Class-II with low solubility and high permeability. The solubility of indomethacin is enhanced by complexing with cyclodextrins. The inclusion complexes of indomethacin were prepared by various techniques using HP β cyclodextrin in various ratios (1:1, 1:1.5, 1:2 and 1:2.5). Solubility study of indomethacin was performed in which highest was observed for 1:2 ratio. The selected inclusion complexes were then utilized for the preparation of film by solvent casting method using HPMC 15 Cps as a film forming agent and PEG-400 as plasticizer. Six formulae were prepared and evaluated for *in vitro* dissolution characteristics, *in vitro* disintegration time, and their physico-mechanical properties. The promising film (F4) showed greatest drug dissolution (more than 75% within 15 min), satisfactory *in vitro* disintegration time (45 sec) and physico-mechanical properties that are suitable for mouth dissolving films. By complexation taste masking also improved. Optimized mouth dissolving film was compared with marketed product by similarity and dissimilarity factors.

INTRODUCTION

Development of new drug delivery systems has been one of the major thrust areas of pharmaceutical research. The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body to promptly achieve and then maintain the desired concentration. An ideal fast dissolving delivery system should have the following properties: High stability, transportability, ease of handling and administration, no special packaging material or processing requirements, no water necessary for application, and a pleasant taste. Therefore, they are very suitable for pediatric and geriatric patients; bedridden patients; or patients suffering from dysphagia. This novel drug delivery system can also be beneficial for meeting current needs of the industry. Mouth dissolving films (MDF) were initially introduced in the market as breath fresheners and personal care products such as dental care strips and soap strips.

Indomethacin is a non-steroidal anti-inflammatory agent (NSAIA) with anti-inflammatory, analgesic, antipyretic activity. Its pharmacological effect is thought to be mediated through inhibition of the enzyme cyclooxygenase (COX), the enzyme responsible for catalyzes the rate-limiting step in prostaglandin synthesis via the arachidonic acid pathway. It is commonly used as an analgesic and anti-inflammatory agent. Indomethacin belongs to class-II drug have low solubility and high permeability (log P value is 3.53).

The goal of present study is to formulate and characterize the indomethacin cyclodextrin loaded mouth dissolving film by using polymers like Hydroxy Propyl methyl cellulose of different grades to enhance the permeability and consequently solubility.

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MATERIALS AND METHODS

Materials

Indomethacin, hydroxy propyl beta cyclodextrin (HPβCD), hydroxy propyl methyl cellulose (HPMC), sodium starch glycolate (SSG), saccharin, poly ethylene glycol (PEG), menthol.

Construction of calibration curve for Indomethacin

The calibration curve for Indomethacin was constructed in phosphate buffer solution of pH 7.2±0.05.

Preparation of stock solution

Indomethacin (100 mg) was weighed accurately and dissolved in ethanol and the volume was made up to 100 mL with the same solvent in a volumetric flask.

Preparation of phosphate buffer solution pH 7.2±0.05

Phosphate buffer solution was prepared by mixing 250 mL of 0.2 M KH_2PO_4 and 175 mL of 0.2 M NaOH and make up with distilled water up to 1000 mL.

Preparation of working standard solutions

From the stock solution, 0.5, 1, 2, 3, 4 and 5 mL of the solutions were taken into 100 mL volumetric flasks and were made up to the volume using Phosphate buffer solution of pH 7.2±0.05, to get solutions of 5, 10, 20, 30, 40 and 50 µg/mL concentrations respectively. The absorbance of the above dilutions was determined, at 318 nm, using UV spectrophotometer against Phosphate buffer solution of pH 7.2±0.05 as the blank. The results are tabulated in (Table1).

A calibration curve (Figure 1) was constructed by plotting the absorbance against the concentration of indomethacin. A regression equation was derived from the plot, which was used for the estimation of indomethacin in Phosphate buffer solution of pH 7.2±0.05.

The method obeyed Beer's law in the concentration range of 5-50 µg/mL and is suitable for the estimation of indomethacin from different sample solutions. The correlation coefficient value (r) was found to be 0.996 indicating a positive correlation between the concentration of indomethacin and the corresponding absorbance values. The regression line describing the relation between concentration and absorbance was as follows.

Y = 0.0181 X + 0.0221

Where, Y is the absorbance at 318 nm and

X is the concentration of indomethacin in µg/mL.

Table 1 Data for standard indomethacin plot

Concentration (µg/mL)	Absorbance
0	0.000±0.00
5	0.097±0.01
10	0.220±0.03
20	0.388±0.05
30	0.614±0.04
40	0.741±0.01
50	0.894±0.06

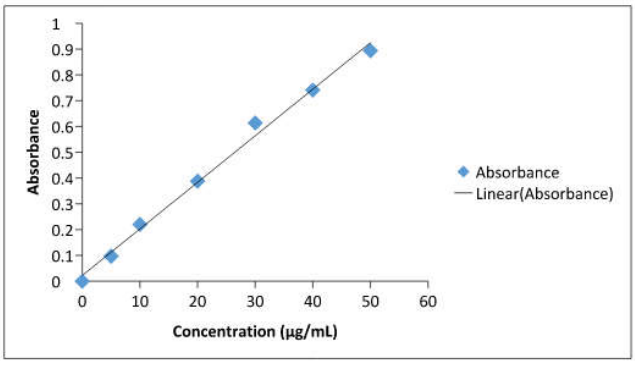


Figure 1 Calibration plot for indomethacin

Drug-Excipient Compatibility Study

FTIR spectra of pure drug, polymers used, and excipients were recorded using FTIR Bruker alpha system with spectrum opus 6.5 software Spectrophotometer to confirm the compatibility between drug and excipients. Sample powder was thoroughly mixed by triturating with all excipients in a glass mortar with pestle and FTIR spectra of all the samples were recorded over a spectral region from 4700 to 400 cm^{-1} using 20 scans with 4 cm^{-1} resolution.

Preparation of Inclusion Complex

Indomethacin-hydroxy propyl beta-cyclodextrin inclusion complex at molar ratio (1:1, 1:1.5, 1:2, 1:2.5) were prepared by physical trituration, kneading and solvent evaporation method. Prepared products were obtained by dissolving the drug in ethanol. Then the required moles of HP-β-Cyclodextrin in hot distilled water were added dropwise into the solution with continuous stirring for one hour, then the formed complexs were dried under vaccum, then the dried solid mass was stored in desicator under vaccum to a constant weight. Then the product was removed, pulverized and passed through sieve no 100 and the product was stored.

Formulation of indomethacin MDF: (table 2- *composition of indomethacin mdf)*

A series of mouth dissolving film composed of different proportions and combinations of HPMC K100M, and HPMC 15cps was mixed with 5ml of water, SLS was mixed with 5ml, to this SSG(sodium starch glycolate) was added and thoroughly mixed.to this the drug complexes (1:2) was added and thoroughly mixed. To this 50 mg of menthol mixed in 3ml of water and citric acid was added. And then add 50mg of saccharin mixed in 3ml of water. Add this solution to HPMC solution and was mixed continuously for few minutes till all the contents became uniform.

To a Petri dish whose area was known is taken and glycerin was applied so that the film does not stick to it. The above prepared solution was poured into the glycerin applied Petri dish and was made sure that the solution was uniformly spread. This was kept in hot air oven for 24 hrs. At 50°C.After 24 hrs the petridish with the film was removed. The film was removed and was cut into dimensions of 2x2 cm^2 and was assessed.

Table 2 Composition of indomethacin MDF

INGREDIENTS	F1	F2	F3	F4	F5	F6
IND/HP β-CD	1:2	1:2	1:2	1:2	1:2	1:2
HPMC(K100M)MG	50	100	150	-	-	-
HPMC 15CPS	-	-	-	300	400	450
SLS	50	100	200	50	200	200
SSG	200	200	200	200	200	200
MENTHOL	50	50	50	50	50	50
SACCHARIN	50	50	50	50	50	50
CITRIC ACID	15	15	15	15	15	15
PEG 400(ML)	0.5	0.5	0.5	0.5	0.5	0.5

Evaluation of indomethacin MDF

Indomethacin MDFs were evaluated for uniformity of weight (Shimadzu Electronic Balance, Japan), thickness of film (Dial Gauge, model: K17, accuracy 0.001 mm, Baker Precision Measuring Instruments, China), surface pH, weight variance and thickness, folding endurance, drug content, moisture content, moisture absorption, *invitro* release study.

Uniformity of Weight

Each film was individually weighed on analytical balance (Shimadzu Electronic Balance, Japan) and average weight of 3 films was found. A large difference in weight denotes the non-uniform distribution of drug in the film.

Thickness of Film

The thickness of the different films was measured using a calibrated dial gauge (Baker Precision Measuring Instruments, China) with an accuracy of 0.001 mm. Thickness was measured by placing each film between the anvil and the presser foot of the dial gauge in 5 different locations and the average thickness was calculated.

Surface pH of films

Either highly acidic or highly basic pH of MDF would cause discomfort on administration. To know the surface pH of the film, the film was placed in a Petri dish and was moistened with 0.5 mL of distilled water and kept for 30 sec. The surface pH was measured by means of pH paper placed on the surface of the swollen films. The average of 3 determinations for each formulation was found out.

Folding endurance

The folding endurance was determined manually for the prepared film by repeatedly folding the film at the same place until it broke. The number of times the film could be folded at the same place without breaking or cracking gave the value of folding endurance.

Drug content

The drug content in the mouth dissolving film were determined by dissolving 2 cm^2 film in 100 ml phosphate buffer (pH 7.2) and shaken vigorously for 24 hrs at room temperature. These solutions were filtered through Whatman filter paper (No.42). After proper dilution, the samples were analyzed by UV-Vis spectrophotometer at 318 nm against blank.

Moisture content and moisture absorption

The films were weighed accurately and kept in desicator containing anhydrous calcium chloride. After 3 days, the patches were taken out and weighed. The moisture content (%) was determined by calculating moisture loss (%) using formula:

$$\text{Moisture content (\%)} = \frac{initial weight - Final weight}{initial weight} \times 100$$

$$\frac{initial weight - Final weight}{initial weight} \times 100$$

The films were weighed accurately and placed in the desicator containing 100 ml of saturated solution of aluminium chloride, which maintains 76% and 86% relative humidity (RH). After 3 days, the films were taken out and weighed. The percentage moisture absorption was calculated using the formula:

$$\text{Moisture absorption (\%)} = \frac{Final weight - Initial weight}{Initial weight} \times 100$$

$$\frac{Final weight - Initial weight}{Initial weight} \times 100$$

In vitro release study

The prepared films were subjected to dissolution study, the invitro release study was performed by using USP dissolution apparatus paddle type and is rotated at 50 rpm at 37°C using pH 7.2 phosphate buffer. The prepared films are placed in the baskets containing 900ml of phosphate buffer and at regular time intervals of 5,10,15,20,30 5ml of samples are withdrawn from each solution and measured for absorbance uv spectrophotometrically at 318 nm. Every time after withdrawal of 5ml of solution it was replaced with 5ml of fresh solution. The readings were noted and calculations were made.

In vitro release kinetic studies

The mechanism of drug release from the formulations during the dissolution in pH 7.2

Phosphate buffer was determined using

- First order
- Zero order

Zero order equation

This equation describes the systems where the release rate is independent of the concentration of the dissolved species. The dissolution data are fitted into the zero order equation:

$Q = Q_0 . K_0 t$

Where,
Q = Amount of drug released at time t
Q_0 = Amount of drug released initially
K_0 = zero order rate constant

A graph of concentration vs. time would yield a straight with a slope equal to K_0 and the

Intercept at the origin of the axis. The zero order plots is derived from plotting the cumulative

Percent drug dissolved vs. time.

First order equation

The First order equation describes the release from systems where the dissolution rate is dependent upon the concentration of the dissolving species.

Release behavior generally follows the following first order release equation

$\ln M = \ln M_0 - K_1 t$

Where,
M is the amount of drug undissolved at time t,
M_0 is the amount of drug undissolved at t = 0
K_1 is the corresponding release rate constant

A graph of log concentration of drug remaining vs. time a straight line with a negative slope

Determination of difference and similarity factors:

The *in vitro* drug release profile of the formulations (test) was compared with the theoretical release profile (reference) of marketed capsules of indomethacin by determining the 'difference factor', f1 and 'similarity factor' f2. The difference factor (f1) measures the percent error between the two curves over all time points and was calculated by using the following Eq.

$$f1 = \frac{\Sigma(Rj - Tj)}{\Sigma Rj} X\ 100 f1 = \frac{\Sigma(Rj - Tj)}{\Sigma Rj} X\ 100$$

Eq.1

$$f2 = 50\ X\ log\ \{[1 + {}^{1}/_{n}\ \Sigma(Rj - Tj)2^{-0.5}]X\ 100\}$$
$$f2 = 50\ X\ log\ \{[1 + {}^{1}/_{n}\ \Sigma(Rj - Tj)2^{-0.5}]X\ 100\}$$

Eq.2

The similarity factor (f2) is a logarithmic transformation of sum of squared error of differences between the test Tj and the reference products Rj over all time points. It was calculated

based upon Eq. 2. In order to consider the similar dissolution profiles, f1 value should be lower than 15 (i.e. 0–15) and f2 value higher than 50 (i.e. 50 -100). In the present investigation, f1 and f2 were calculated for optimized formulations against theoretical release profile of the respective drugs.

RESULTS AND DISCUSSION

Solubility Studies

The solubility values of indomethacin, indomethacin/ HP β CD inclusion complexes are shown in (**Table 3**). Each of the three preparation methods could increase the solubility of indomethacin but to a different extent. Solvent evaporation method produced the highest solubility of indomethacin in HP β CD than the physical mixing and kneading method.

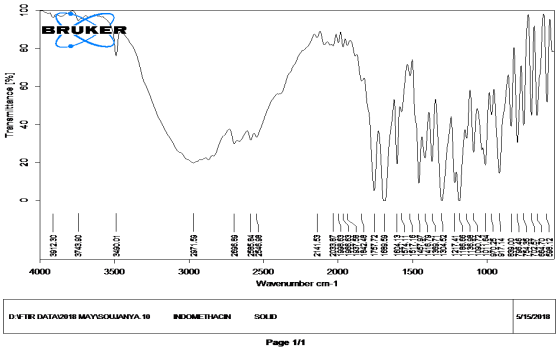
For each preparation method, the concentration of HP β CD used to solubilize indomethacin was critical. In all the cases it was observed that solubility was gradually increase until 1:2 of HP β CD , indicating further no need of solubility enhancer for drug solubilization.

Table 3 solubility values of indomethacin, indomethacin/ HP β CD inclusion complexes

Code	Indomethacin: cyclodextrin	Solubility
IND	IND:NO HP β CD	0.12±0.11
ICD 1:1(PT)	IND: HP β CD(1:1)	0.18±0.08
ICD 1:1.5(PT)	IND: HP β CD(1:1.5)	0.42±0.21
ICD 1:2(PT)	IND: HP β CD(1:2)	0.53±0.15
ICD 1:2.5 (PT)	IND: HP β CD(1:2.5)	0.51±0.07
ICD 1:1(KM)	IND: HP β CD(1:1)	0.98±0.07
ICD 1:1.5(KM)	IND: HP β CD(1:1.5)	1.23±0.82
ICD 1:2(KM)	IND: HP β CD(1:2)	1.42±0.03
ICD 1:25 (KM)	IND: HP β CD(1:2.5)	1.40±0.08
ICD 1:1 (SE)	IND: HP β CD(1:1)	1.11±0.28
ICD 1:1.5 (SE)	IND: HP β CD(1:1.5)	1.32±0.03
ICD 1:2(SE)	IND: HP β CD(1:2)	1.58±0.72
ICD 1:25 (SE)	IND: HP β CD(1:2.5)	1.53±0.19

Drug-Excipient Compatibility Study

FT-IR spectra of indomethacin, HP β CD, inclusion complex, and dry mix of MDF are given in (figure 4) The FTIR spectrum of pure indomethacin(figure 2) drug showed characteristic peaks of aromatic C-N stretching at 1610.35 cm^{-1}, C=O stretching at 1610.35cm^{-1}, O-H stretching at 1220.05 cm^{-1}. The obtained FTIR spectrum thus confirms the purity of the drug.

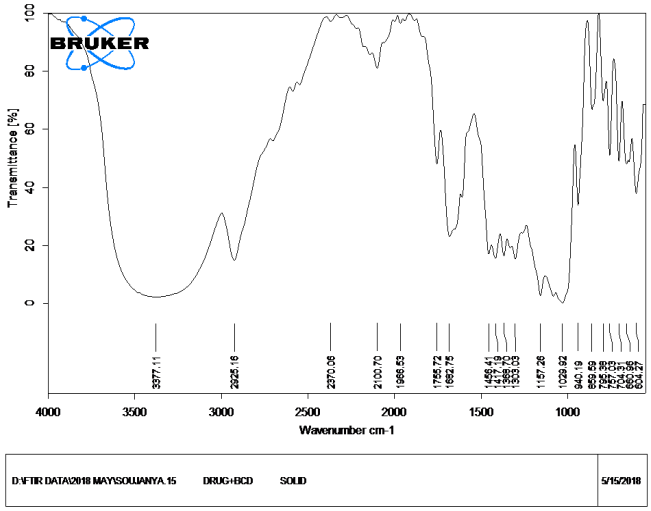


Functional group	Reported frequency(cm^{-1})	Observed frequency(cm^{-1})
C-N	1600-1700	1610.35
C=O	1600-1900	1610.35
O-H	1200-1500	1220.05
C-H	1300-1500	1369.67

Figure 2 FT-IR spectrum of indomethacin

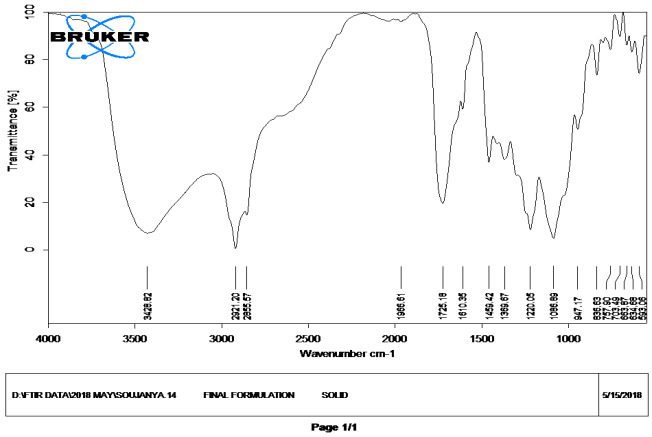
The FTIR spectrum of hydroxy propyl beta-cyclodextrin (figure 3) shows prominent peaks of O–H stretching vibration at 1220.05 cm^{-1}. C– H stretching and C–O stretching vibrations were observed at 1367.69 cm^{-1} and 1610.35 cm^{-1} respectively.

The IR spectrum of indomethacin-HP β-cyclodextrin complex bears the peaks corresponding to the indomethacin peaks as well as that of HP beta-cyclodextrin with no significant shift in the major peaks. The FTIR spectrum of dry mix of indomethacin MDF shows all the prominent peaks of indomethacin indicating the maintenance of identity of the drug and thus the stability of the drug in film.



Functional group	Reported frequency(cm^{-1})	Observed frequency(cm^{-1})
O-H	1200-1500	1303.03
C=O	1600-1900	1682.75
O-H	1200-1500	1220.05
C-H	1300-1500	1368.70

Figure 3 FT-IR spectrum pf indomethacin-HP β CD complex



Functional group	Reported frequency(cm^{-1})	Observed frequency(cm^{-1})
C-N	1600-1700	1610.35
C=O	1600-1900	1610.35
O-H	1200-1500	1220.05
C-H	1300-1500	1369.67

Figure 4 FT-IR spectrum of final formulation (dry powder):

Invitro dissolution of inclusion complexes

The mean dissolution profiles of indomethacin and HP β -cyclodextrin inclusion complexs produced using three different

preparation methods they are physical trituration, solvent evaporation and kneading method. The dissolution of indomethacin was below 40% while the dissolution of indomethacin/ HP β CB complex was more than 70% at 15 mins in the solvent evaporation method at 1:2 ratio. The results showed in (table4) that formation of inclusion complex by solvent evaporation method improved indomethacin dissolution than the physical trituration and kneading method. Graph is plotted between time verses cumulative percent drug release in (figure 5).

Table 4 drug release data of indomethacin (pure drug) and indomethacin – HP β CD prepared by solvent evaporation method

time(min)	cumulative percent drug release(%) of ind/HP β CD complex by solvent evaporation method				
	Ind	ind(1:1)	ind(1:1.5)	ind(1:2)	ind(1:2.5)
0	0	0	0	0	0
5	14.97	35.14	39.81	51.85	49.13
10	19.42	44.28	54.19	67.39	67.17
15	23.67	57.28	59.32	75.34	74.42
20	26.54	74.02	79.92	84.06	82.45
30	32.17	83.29	85.02	95.37	93.02
45	31.13	82.65	84.67	94.03	91.98
60	30.54	81.14	82.11	93.97	90.21

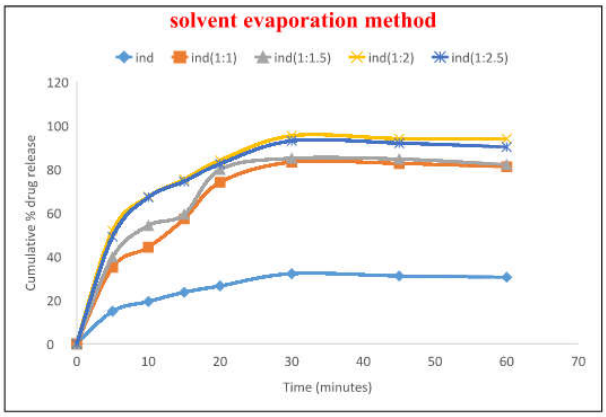


Figure 5 Dissolution profiles of indomethacin from indomethacin – HP β CD complex prepared by solvent evaporation method

Invitro drug release of prepared formulation

The prepared six formulations are subjected to *invitro* dissolution in dissolution apparatus USP paddle type. The samples are withdrawn every five minutes interval up to half an hour. Then they are analyzed UV spectrophotometrically at 318 nm. The values are tabulated in (table 5) and graph plotted between time and percent drug release (figure 6) shows 80% drug release at 20 mins. Among all the formulations F5 shows the maximum drug release.

Table 5 Drug release profiles of indomethacin from indomethacin-HP β CD complex loaded mouth dissolving films

Time (mins)	Cumulative percent drug release (%)					
	F1	F2	F3	F4	F5	F6
0	0±0.00	0±0.00	0±0.00	0±0.00	0±0.00	0±0.00
5	27.2±0.16	29.5±0.15	29.7±0.45	32.6±0.15	43.6±0.12	40.7±0.29
10	32.7±0.28	42.9±0.34	34.9±0.63	41.7±0.25	71.6±0.23	65.7±0.17
15	41.7±0.31	55.7±0.23	46.2±0.54	54.9±0.36	79.6±0.11	69.9±0.29
20	58.5±0.21	78.6±0.41	59.5±0.39	68.5±0.13	86.4±0.07	71.8±0.16
25	65.8±0.43	82.7±0.13	69.7±0.12	75.8±0.64	93.6±0.16	78.9±0.24
30	78.9±0.21	90.7±0.23	80.2±0.23	82.2±0.12	98.3±0.27	84.4±0.29

Mean± SD (n=6)

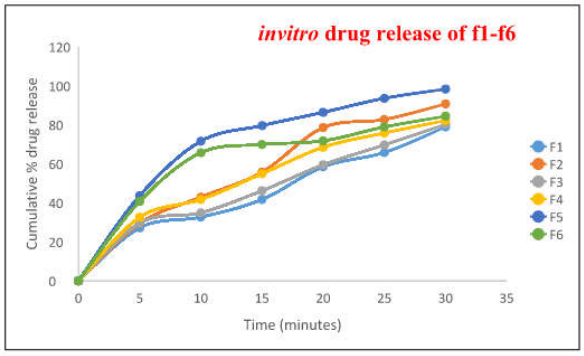


Figure 6 Dissolution profiles of indomethacin from indomethacin-HP β CD complex loaded mouth dissolving films

Evaluation parameters of MDF

The film evaluation (Table-6) indicates that the weight variation of these formulated mouth dissolving films varied between 2.02±0.03 to 2.73±1.02. The thickness of these films varied between 0.21±0.12 to 0.27±0.83 mm, the thinnest formulation F2 and F5, The thickest formulation F6 Folding endurance was measured manually. The highest folding endurance was observed in case of F1 (92) and the lowest in the case of F6 (82). The range of folding endurance study ensured flexibility of these formulated mouth dissolving films. The drug content (%) in all formulations varied between the ranges 98.02±0.16 to 99.45±0.24. this indicates that the drug dispersed uniformly throughout the polymeric film.

The moisture content (%) study was done for 3 days. The percentage of moisture content (%) is varied between 1.76±0.24 to 4.13±0.11. in most cases, the moisture uptake content was found to increase with increasing concentration of polymers that are more hydrophilic in nature. The low moisture content in the formulation is highly appreciable to protect from microbial contaminations and bulkiness of the films. A low moisture content in the formulations helps them to remain stable from being a completely dried and brittle film.

Table 6 physicochemical evaluation of indomethacin - HPβCD loaded Mouth dissolving films

Formulations	Weight variation* (g)	Thickness* (mm)	Folding endurance	Drug content* (%)	Moisture content (%)	Moisture uptake %
F1	2.02±0.03	0.21±0.12	92±0.23	98.02±0.16	3.64±0.33	4.09±6.03
F2	2.13±0.13	0.23±0.63	90±0.73	99.19±0.43	3.92±0.23	4.12±0.08
F3	2.35±0.18	0.27±0.83	85±0.63	99.23±0.23	4.13±0.11	5.26±0.78
F4	2.47±0.53	0.21±0.93	89±0.43	98.43±0.27	1.76±0.24	2.01±0.67
F5	2.58±0.98	0.24±1.22	90±0.09	99.45±0.24	2.76±0.03	2.79±1.23
F6	2.73±1.02	0.27±0.09	82±0.23	98.06±0.03	2.99±0.13	3.07±0.91

In vitro release kinetics

In order to predict and correlate the release behavior of indomethacin from different films, it is necessary to fit into a mathematical model. The *in vitro* drug release data from mouth dissolving films were evaluated kinetically using various mathematical models like zero order and first order (figure 7) and for marketed products was shown in (figure 8 and figure 9) by observing the regression coefficient values the drug release from the dosage form follows zero order independent of the concentration.

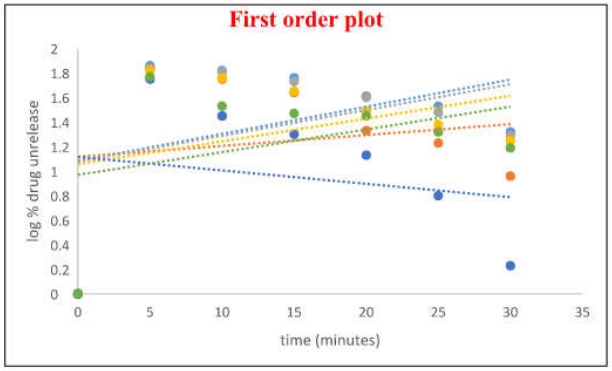


Figure 7 First order plot of prepared indomethacin-HP β CD loaded Mouth dissolving films

Figure 8 Zero order plot of marketed formulation of indomethacin (indocap)

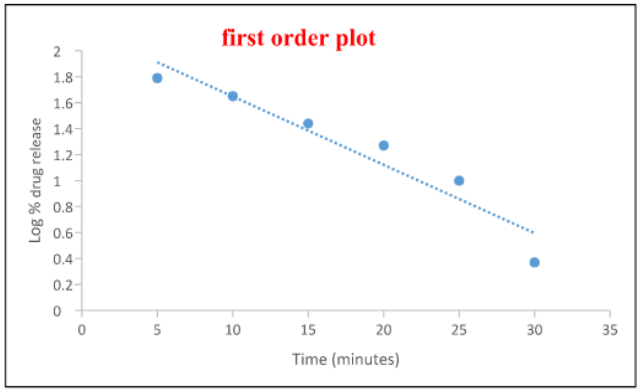


Figure 9 First order plot of marketed formulation of indomethacin (indocap)

Comparison of optimized formulation with marketed product

A comparison of the release of commercial and formulated indomethacin-HP βCD loaded mouth dissolving film (F5) (figure 10) (table 7) by employing HPMC 15cps (350mg), SSG(150mg) and PEG 400 (0.5ml) contain drug/HP β CD (1:2), where drug equivalent amount of 25mg were compared. Drug release profiles of F5 (Test) and indocap (Reference) were compared by calculating difference factor f_1 and similarity factor f_2. A value of f_1<15 and f_2>50indicates similarity of two drug release profiles. The values of f_1 and f_2 were found (table 8) to be 8.7 and 53.5 respectively. The value of the difference factor (F1) 8.7 (between 0-15); and similarity factor (F2) 53.5(> 50) indicates excellent equivalence in performance between the developed test products and the reference marketed product.

Table 7 Drug release data for selected indomethacin- HP β CD loaded mouth dissolving film and commercial capsule

Time (min)	Marketed Product Indocap	F5
0	0.00±0.00	0.00±0.00
5	37.42±0.05	43.61±0.12
10	54.93±0.17	71.63±0.23
15	72.16±0.15	79.68±0.11
20	81.28±0.21	86.45±0.07
25	89.82±0.07	93.61±0.16
30	97.62±0.09	98.39±0.27

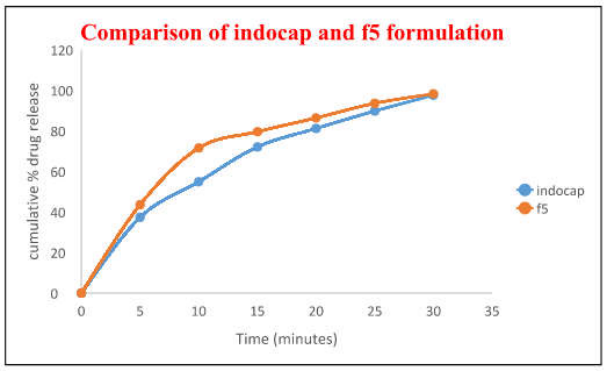


Figure 10 Drug release profiles of indomethacin – HP β CD loaded mouth dissolving film (f5) prepared and commercial capsule

Table 8 Evaluation of f1 and f2 for the comparison of drug release profile of formulation F5 and commercial product (indocap)

Time (min)	Percent drug dissolved			
	Indocap (Reference)	F5	$R_j - T_j$	$[R_j - T_j]^2$
0	0	0	0	0
5	37.4	43.6	6.2	38.44
10	54.9	71.6	16.7	278.89
15	72.1	79.6	7.5	56.25
20	81.2	86.4	5.2	27.04
25	89.8	93.6	3.8	14.44
30	97.6	98.3	0.7	0.49
N=6		=473.1	=40.1	=415.55

Stability Studies

Stability studies were conducted for the best Formulation F2 as per ICH guidelines for a period of 3 months and the results were shown in (Table-9). The results indicate that there is no significant change in, Physical appearance, Folding endurance, Moisture uptake. However, there is a slight variation in the *In vitro* drug release. It was concluded that the films were stable during the study period.

Table 9 Stability studies of the best Formulation (F5)

Sampling time	Physical appearance	Folding endurance	Moisture uptake	*In vitro* drug release
Initial	Transparent	82	3.28	98.68
After 1 month	Transparent	82	3.27	97.72
After 2 month	Transparent	82	2.91	97.23
After 3 month	Transparent	82	2.89	96.91

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How to cite this article:

Maha Lakshmi J *et al* (2018) 'Formulation And Characterization of Indomethacin Cyclodextrin Loaded Mouth Dissolving Films', *International Journal of Current Advanced Research,* 07(8), pp. 15110-15117.
DOI: http://dx.doi.org/10.24327/ijcar.2018.15106.2757

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