International Journal of Applied Pharmaceutics

ISSN- 0975-7058 Thematic Special Issue 2022

Original Article

APPLICATION OF 3^2 CENTRAL COMPOSITE DESIGN FOR THE FORMULATION OF RAPID SOLUBLE ORODISPERSIBLE FILM OF DIPYRIDAMOLE

FAZIL AHMAD

Department of Anesthesia Technology, College of Applied Medical Sciences in Jubail, Imam Abdulrahman Bin Faisal University, P. O. Box 4030, Jubail, Saudi Arabia
***Email: fmahmad@iau.edu.sa**

Received: 18 Apr 2021, Revised and Accepted: 31 May 2022

ABSTRACT

Objective: The aim of this investigation is to formulate, design, optimize and to an evaluation of the rapid soluble orodispersible film (OTF) of dipyridamole (DPI) using the solvent casting method by 3^2 central composite designs.

Methods: Statistical design was used to optimize the preliminary formulations by selecting independent variables such as a polymer (HPMC-$E_5$2V, X_1) and plasticizer (PEG400, X_2) concentration as film-forming polymer and as a plasticizer and the dependent variables such as the release of drug in percentage (Y_1), time of disintegration (sec, Y_2) and tensile strength (N/m^2 Y3).

Results: The content of the drug was resulted in the range of 95.05–101 %. The physical properties were found to be colorless and homogenously clear and smooth surface. The folding endurance shown as without any scratches with the pH ranges from 6.35 to 6.75 and the prepared film was not irritated to the oral mucosa.

Conclusion: The prepared films showed an optimum time of disintegration that is 25 sec, 96.74% drug release in phosphate buffer of pH 6.8 at initial 5 min and 85.98 % *ex-vivo* permeation studies after 30 min.

Keywords: Dipyridamole, Tensile strength, Solvent casting method, HPMC E_2V5, Rapid soluble films

DOI: https://dx.doi.org/10.22159/ijap.2022.v14ti.39 Journal homepage: https://innovareacademics.in/journals/index.php/ijap

INTRODUCTION

Currently, orodispersible films (ODF) has gained abundant attention amongst all the oral drug delivery systems. Subsequently, ODF has a limited application, such as swallowing difficulties alone, but it offers too much of benefits, such as the probability to adjust the requirements of dosing for a subgroup of patients. In contrary, oral liquid for administration, drug liquefies in the mouth (1-30 sec.) owing to flexibility and comfortability. In another hand, rapid soluble oral films (FDOFs) interest increased because of the better bioavailability, including absorption and permeation via the drug dissolves in mucosal saliva within a minute and it does not required any supporting solvent for oral administration (i.e. water) [1]. From the reviews from the patient's compliance, rapid soluble products i.e., oral thin films (OTFs) are alternative and it superior to that of rapid soluble dosage forms. The OTF technology, nothing but film form delivery that is defined, is an emerging trend in the pharmaceutical formulation for the preparation of rapid soluble dosage forms [2]. Commercially, the OTFs technology has introduced the film having drugs and it facilitates the permeation rate around 5-1000-fold higher in oral mucosa to than that of the skin. FDOFs are very essentials in pediatrics, geriatrics, bed ridden, emetic, diarrhea, and coughing or unexpected incident of allergic attacks and the active lifestyle patients. The shelf life of OTF has been reported around 2–3 y based on the drug present in the system, however, which is profound efficient to the humid environment [3]. The mechanism of OFT system consist of very thin stripe, which has been placed under the tongue or mucosal tissues, which could deliver the drug rapidly by wetting and hydrating the film in saliva or mucous and sticking on the site of application [4].

Dipyridamole is inhibits platelets. It is used as an antithrombotic agent in clinical practice. DIP has a biological half-life of only 2-3 h. Dipyridamole (DIP) oral dose formulations have a varied absorption profile, with bioavailability ranging from 11 to 44%. Dipyridamole has a pH-dependent solubility at 37 °C, with good solubility at lower pH (36.5g-L at pH 1.0) and poor solubility at higher pH (0.02g-L at pH 7.0).

The stomach and duodenum are the chief absorption sites of Dipyridamole, it should be given regularly or as a sustained-release (SR) preparation due to its short biological half-life of 2 to 3 h. In this current study, a quick soluble orodispersible film of Dipyridamole was attempted to prepare a stable formulation with rapid disintegrates and dissolves to release the drug for absorption at oral mucosa, which maintains the immediate soluble characteristics and it is allowed GIT absorption while oral administration, in contrast with rest of the rapid dissolving (lipophylisates) dosage forms [5, 6]. The molecular structure of DIP and the advantages of its oral thin film is represented in fig. 1.

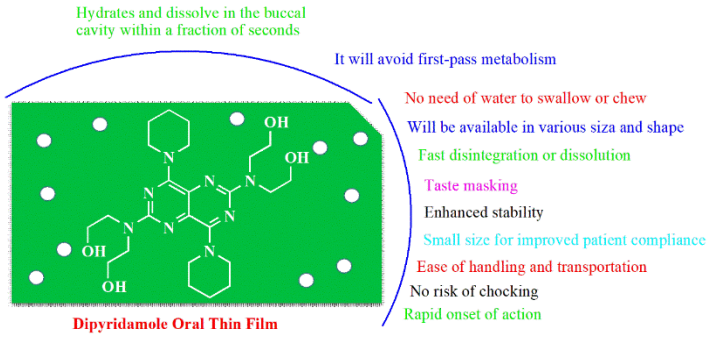


Fig. 1: The molecular structure of DIP and advantages of DIP oral disintegrating film

MATERIALS AND METHODS

Dipyridamole (DIP) was obtained from MSN Laboratories Pvt. Ltd. Hyderabad (India) as a gift sample. Hydroxypropyl methylcellulose $E_5$2V, PEG400, citric acid, sodium saccharin, methanol, and ethanol, chloroform, and peppermint oil was purchased from SD Fine Chem limited, Mumbai, India. Freshly prepared distilled water and analytical grade material was used throughout the study.

Pre formulation study

The physicochemical compatibility of drug and the materials used this study were performed by Differential Scanning Calorimetry (DSC) and Fourier Transform Infrared (FT-IR) Spectroscopy method as described by Gill *et al*., 2010 [7] FT-IR is a tool by which we can identify the change in functional groups of drug and excipients after mixing.

Preliminary trials for formulation of film

Selection of polymers

The HPMC $E_5$2V and plasticizer (PEG400) were used for the preparation of rapid soluble ODFs. HPMC $E_5$2V (40-50 %) does not produced a good result (the film was not easily peelable), whereas the film of HPMC in the range of 35-30% concentration also did not show good results (film weighed more). The concentration of HPMC $E_5$2V in the range of 25% does not give good results (the film was sticky in nature). Many trials were done on different polymers like HPMC 15cps (weight is very less), HPMC LV (due to its low viscosity film was sensitive in nature), whereas HPMC K_{100} (weight of film is very thick) [8-10]. By the above preliminary studies, the percentage of HPMC $E_5$2V between 10-20 % was chosen for the film's formulation.

Selection of plasticizers

Selection of best compatible plasticizer is a critical step for the formulation of the films. Numerous plasticizers were chosen, and trials were performed, it was observed that from the varieties of plasticizers like polyethylene glycol, propylene glycol and glycerin are commonly used plasticizers for the formulation of film [11, 12]. Propylene glycol (>15%) does not show film properties of folding endurance, whereas polyethylene glycol (PEG 200) has not given good results as was tested for thickness, polyethylene glycol (PEG300) formed superior transparent film and had least water rate of vapor permeation. By the preliminary trials, it was concluded that polyethylene glycol (PEG400) was suitable to make flexible and stable with showed perfect mechanical strength and was identified as the ideal for making film.

Selection of sweeteners

The identification of the compatibility and sweeteners influence on the palatability of OTF, we have studied on aspartame, sucralose, mannitol, and sodium saccharine. Mannitol was not preferred as it not crystallized out when film was dried [13]. A semi-synthetic sucralose was chosen because it is non-carcinogenic, non-toxic, and highly stable, which is a commonly recognized sweetener for several of food and pharmaceutical products [14].

Selection of saliva stimulating agent (SSA)

Currently, SSA is used to increase the saliva secretions; hence, oral film could rapidly dissolve and disintegrate in the oral cavity. Citric acid, lactic acid, mallic acid and ascorbic acid are the saliva stimulating agents [15]. Amongst all the stimulating agents, citric acid was used in present formulation [16].

Selection of flavoring agent

Flavoring agents are the ingredients which impart flavor to any of the formulation. Any US-FDA flavor can be added to the preparation. Flavoring agents should be compatible with the drugs and other excipients. Among all the flavoring agents mint was selected.

Formulation of rapid soluble films

Briefly, Solvent casting method used to formulate rapid soluble film using HPMC (film-forming polymer) and PEG 400 (plasticizer). 10 mg of DPI was added into the polymer solution containing ethanol (0.5 ml), methanol (5 ml) and chloroform (5 ml) with continuous stirring using magnetic stirrer at RPM. Under continuous stirring, 0.5 ml of mint (flavoring agent), sucrose (sweetening agent) and citric acid (saliva stimulating agent) was added.

The homogeneous solution was then cast as a film by poured in a petri plate and allowed the solution to dry at overnight. The dried film cut into pieces of the preferred size and stored in an aluminum foil. The formulation design of rapid soluble film of DPI by solvent casting method is represented in table 1.

Table 1: The formulation design of rapid soluble film of dipyridamole by solvent casting method

Ingredients	Formulation code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Drug (mg)	10	10	10	10	10	10	10	10	10
HPMC E-52v (mg)	100	150	200	100	150	200	100	150	200
PEG 400 (ml)	0.2	0.2	0.2	0.4	0.4	0.4	0.6	0.6	0.6
Ethanol (ml)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Methanol (ml)	2	2	2	4	4	4	6	6	6
Chloroform (ml)	5	5	5	5	5	5	5	5	5
Sucrose (mg)	10	10	10	10	10	10	10	10	10
Citric Acid (mg)	40	40	40	40	40	40	40	40	40
Mint (ml)	1	1	1	1	1	1	1	1	1

Physical characterization

Weight variation and thickness of the film

A calibrated vernier caliper have being used to measure the thickness of the film (Mitutoyo, Japan). A sample was taken that was equal to the drug's dose. The film was placed on the anvil, and the dial reading was recorded. At three different locations, the thickness was measured. For weight variation, 3×3 cm^2 films containing a medication dose were cut and weighed on an analytical scale (Shimadzu Corporation Japan AUX 220). The films of size 3×3 cm^2 were cut from different spots of casted film for the content uniformity test. Each 9 cm2 film was sonicated for 15 min using an ultrasonicator in a volumetric flask containing 60 ml of 0.1 N HCl. After proper dilutions, the volume was increased to 100 ml and the absorbance of the solution was measured using a UV spectrophotometer at 296 nm [17-20].

Moisture absorption on film (MAF)

The physical stability estimation of the prepared oral thin film was determined the percentage of MAF under humid conditions. The accurately weighed films cut into pieces of similar size (2.5 × 2.5 cm^2) were treated with saturated solution of aluminum chloride in a desiccator at maintained humidity of 79.5 % RH. The films were weighed and determined after 96 h of percentage MAF using the following formula [21].

$$\text{MAF} = \frac{\text{Total weight} - \text{initial weight}}{\text{initial weight}}\ 100 \ldots\ldots\ldots (1)$$

Moisture loss on film (MLF)

This test was also used to check the film's integrity at dry conditions. Three 2x2 films were carefully cut and weighted accurately and placed in a desiccator containing fused anhydrous $Cacl_2$ (calcium

chloride). The films were removed and weighed after 72 h. The average percentage moisture loss of three films were determined [22]. The physical rigidity estimation of the prepared oral thin film was determined the percentage of MLF under dry condition. The accurately weighed films cut in to pieces of similar size (2.5 × 2.5 cm^2) were fused with saturated solution of anhydrous calcium chloride in a desiccator at maintained humidity of 79.5 % RH. The films were weighed and determined after 72 h of percentage MAF using the following formula [22].

$$\text{MLF} = \frac{\text{initial weight} - \text{Total weight}}{\text{initial weight}} \text{X}100 \ldots\ldots\ldots\ldots (2)$$

Surface pH

The prepared films surface pH was estimated owing to an irritation property towards buccal mucosa and influence the hydration rate of polymer [23]. It was observed that there is no significant difference in surface pH in any of the formulations, and the pH range is within the salivary pH range (6.5-6.8). Hence, they will not cause irritation and can achieve patient compliance.

Tensile strength

The energy (force) necessary to break a film with the cross-section area was calculated as the tensile strength.

$$\text{Tensile Strength in percentage} = \frac{\text{breaking energy (N)}}{\text{Initial cross section area of the film (mm)}} 100$$

Folding endurance (FD)

It was determined by folding the film repeatedly in the same spot until it broke. FD was determined by broken the film by simply continuous folding at the particular direction; hence the estimation had been done by the number of times the film folded without breaking [24].

Drug content

The prepared film was dissolved using phosphate buffer (PBS, 10 ml, pH 6.8) and the stock solution was sonicated sound until 1 h. from the stock solution, appropriate dilution was made up to 100 mcg using the same solvent and the absorbance was estimated at 291 nm with UV-spectrophotometer [25].

Disintegration time (DT)

The DT was determined using simulated saliva juice i.e., PBS in pH 6.8 at 37±0.5 °C for each film (2.5 x2.5 cm^2). The specification of DT apparatus i.e., petri plate was used as standard specified by the supplier. It was calculated completely based on the film broken into very small pieces in triplicate [26]. The complete break up of film at a different time is represented in fig. 2.

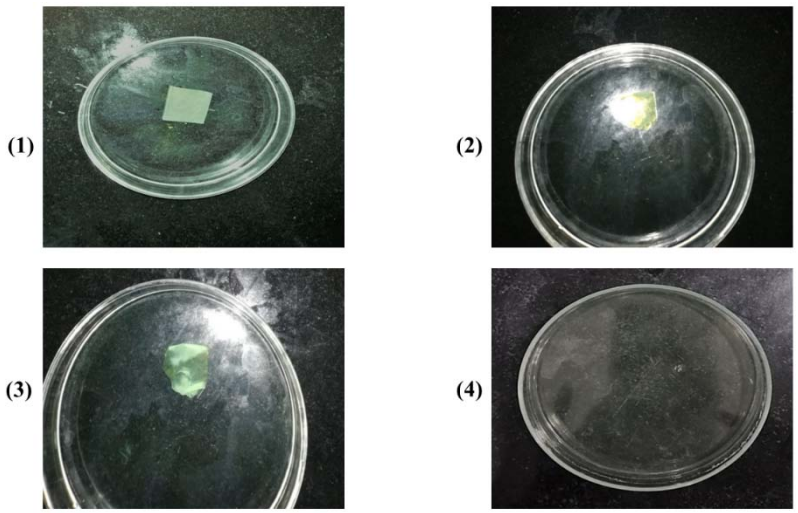


Fig. 2: Disintegration time of (1) 60 sec; (2) 45 sec; (3) 30 sec; and (4) 25 sec

Dissolution studies (DS)

The Dissolution studies was carried out in 200 ml of PBS (pH 6.8) at 37 0.5 °C and 50 rpm using a dissolving apparatus as per Indian Pharmacopoeia specifications (DS 8000, Lab India, India). 5 ml of samples were pumped out and filtered using Whatman filter paper (0.45 m) at a zero-time interval, and samples were deposited into the jar with the above specifications every 5 min until 30 min. A UV spectrophotometer was used to determine the amount of Dipyridamole dissolved in the media. The experiment was replaced with PBS (pH 6.8) to maintain the sink condition, which was a correction for the fresh dilution.

RESULTS AND DISCUSSION

Physical characterization

Physical characterization of the formulated oral thin film was performed in terms of weight variation, thickness, drug content, DT, DS, FD, MAF, MLF surface pH, and tensile strength.

Weight variation of the film

The average weight of OTF film was found in the value of 49.18-39.53 mg. All the batches have passed the weight variation test successfully as per I. P. B. P. and USP. The weight variation data of all the batches are represented in table 2.

Thickness

The average thickness of all the film was found in the value of 0.24-0.65±0.01 mm. It indicates the uniform OTF cast of the batches. Thickness must be uniform throughout the film as it affects the drug content uniformity. The thickness of all the formulated OTF's is represented in table 2.

Drug content

The prepared films were found to contain the uniform amount of DPI representing that the drug was equally dispersed to the OTF. The uniformity of drug content significant with the prepared film is represented in table 2.

Folding endurance

It determines the mechanical strength of the OTFs, the higher the value of folding endurance, higher is the mechanical strength of the film. As per reference, the mechanical strength of the film represents the higher value of folding endurance, from the prepared OTF higher value of 100 times found from table 2**.** These effects are owing to the

polymer and plasticizer used in the formulation of OFT, it is a desired effect during the handling and application of OFT.

MAF and MLF

The MAF study was performed for the physical stability and film integrity at high humid and extreme dry condition, respectively. From the prepared film, F5 shown the higher value of PMA at 12.13±0.09 due to the presence of higher concentration polymer in the film, in the contrary, higher MLF was found from F8 (table 2).

Surface pH

The pH of the film surface was found in the range of 5.21-7.32±0.015 represent that the formulated batch's film surface was not shown any difference (table 2). It is close to the salivary pH, and it does not cause irritation.

Tensile strength

Tensile strength is a chief property of materials to control their mechanical performance. It is the capability of a material to resist tearing due to tension. The films were evaluated for the tensile strength. Tensile strength was high for formulation F7. The tensile strength of the OTFs is represented in table 2.

Factorial design optimization

ANOVA for linear model

The ANOVA responsenses were given in table 3, 4 and 5. The counter plots for response-1, 2 and 3 are given in fig. 3, 4 and fig. 5 respectively. The point prediction and coniramation are given in table 6 followed by table 7.

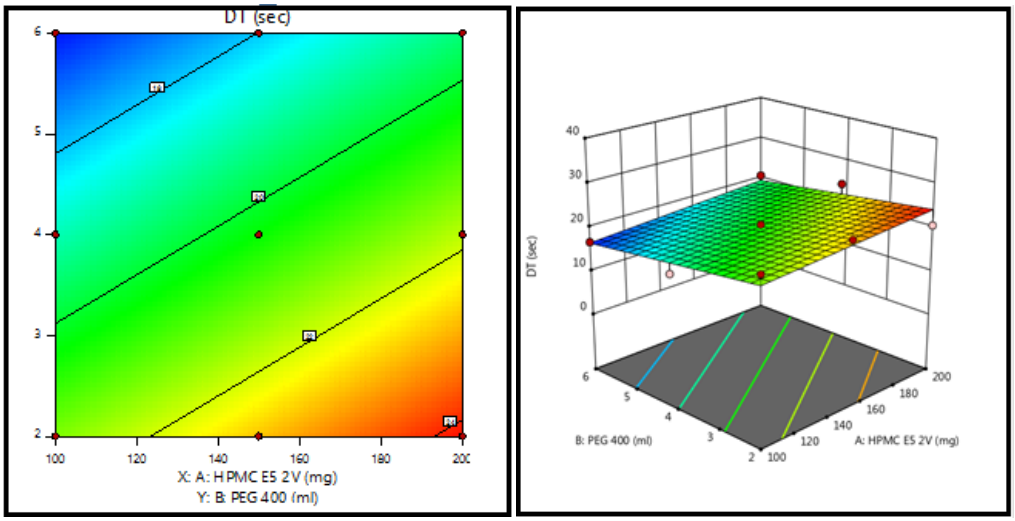
Table 2: Physical characterization of the formulated oral thin film are shown

Formulation code	F1	F2	F3	F4	F5	F6	F7	F8	F9
Wt of Films (mg)±SD	43.9±0.65	41.37±0.92	42.9±0.65	42.12±1.06	41.37±0.85	46.31±0.58	39.53±0.81	49.18±0.9	40.93±1.55
Thickness of Films (mg)±SD	0.24±0.01	0.62±0.01	0.47±0.01	0.59±0.01	0.65±0.02	0.30±0.01	0.44±0.01	0.39±0.01	0.31±0.01
Drug content (%)	96.12±1.02	98. 02±1.32	95.03±2.01	96.01±2.14	92.54±1.34	95±2.02	98.8±2.01	97.21±1.01	94.11±0.01
Time of disintegration (sec)±SD	23.9±1.02	24.2±0.68	16.7±0.93	16.5±0.7	23.6±0.40	20.6±0.76	20.7±0.85	16.4±0.66	20.7±0.93
Folding endurance	102	109	111	120	100	105	110	99	90
PMA±SD	5.21±0.12	10.32±0.11	10.26±0.23	11.23±0.23	12.13±0.09	10.32±0.11	9.24±0.09	7.3±0.04	5.21±0.07
PML±SD	5.97±0.12	5.14±0.72	4.7±0.26	4.14±0.23	4.08±0.03	3.88±0.02	5.71±0.02	6.3±0.04	3.88±0.07
Surface pH±SD	6.73±0.005	6.80±0.005	6.83±0.015	6.64±0.050	6.60±0.015	6.52±0.03	6.67±0.09	7.32±0.04	5.21±0.015
Tensile Strength	0.005	0.006	0.005	0.005	0.004	0.006	0.007	0.004	0.005

Table 3: Response 1-DT

Source	Sum of squares	DF	Mean square	F-value	P-value	
Model	46.22	2	23.11	3.90	0.0322	significant
HPMCE52V	12.33	1	12.33	2.08	0.0493	significant
PEG 400	33.89	1	33.89	5.72	0.0539	significant
Residual	35.55	6	5.93			
COR total	81.77	8				

Counter plot for response-1



[1] **[2]**

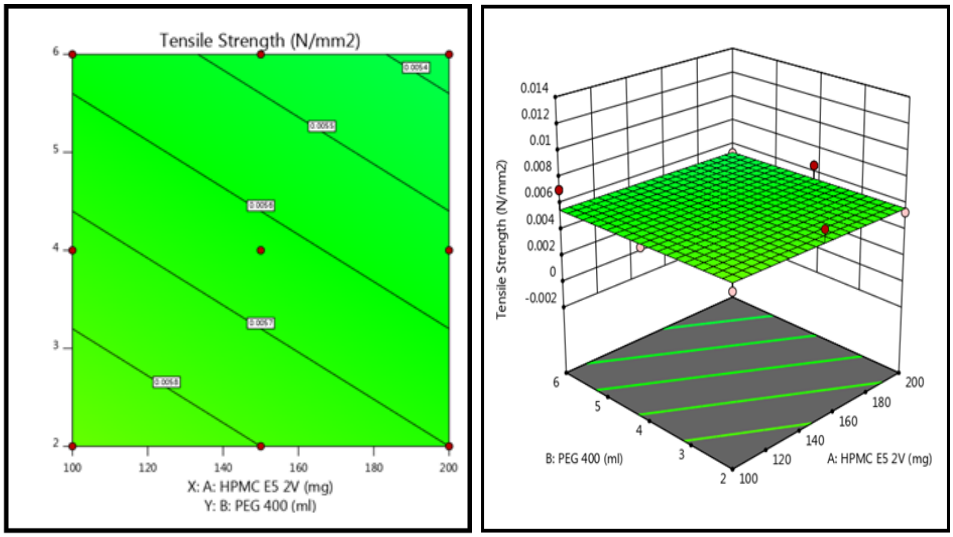
Fig. 3: Counter plots for response-1

ANOVA for linear model

Table 4: Response 2-tensile strength

Source	Sum of squares	DF	Mean square	F-value	P-value	
Model	2.267E-07	2	1.133E-07	0.0857	0.4190	significant
HPMCE52V	6.000E-08	1	6.000E-08	0.0454	0.3384	significant
PEG 400	1.667E-07	1	1.667E-07	0.1261	0.439	significant
Residual	7.933E-06	6	1.322E-06			
COR total	8.160E-06	8				

Counter plots for response-2



[1] **[2]**

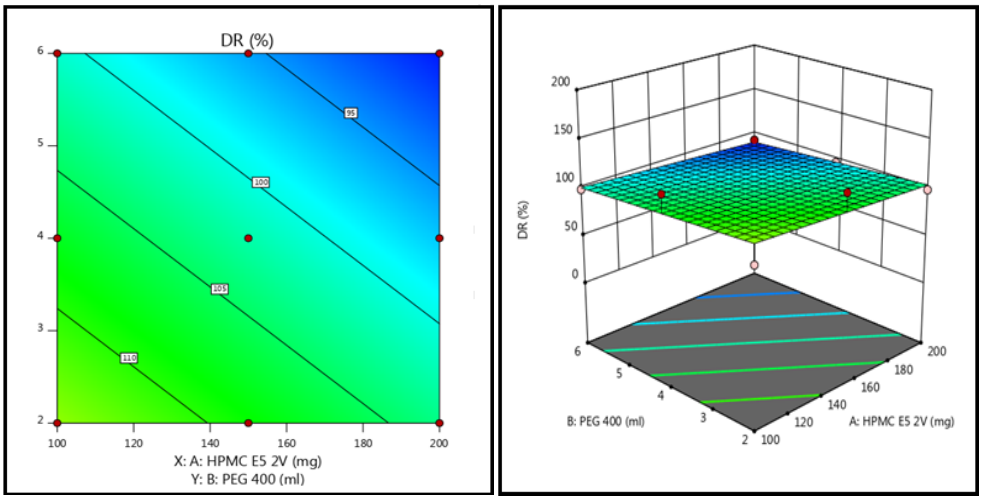
Fig. 4: Counter plots for response-2

ANOVA for linear model

Table 5: Response 3-DR

Source	Sum of squares	DF	Mean square	F-value	P-value	
model	435.73	2	217.86	1.05	0.4064	significant
HPMCE52V	167.06	1	167.06	0.8053	0.4041	significant
PEG 400	268.67	1	268.67	1.30	0.2985	significant
Residual	1244.70	6	207.45			
COR total	1680.43	8				

Counter plots for response-3



[1] **[2]**

Fig. 5: Counter plots for response-3

Table 6: Point prediction

Factor	Name	level	Low level	High level	Std. Div.	Coding
A	HPMC E5 2V	150.00	100.00	200.00	0.0000	Actual
B	PEG 400	4.00	2.00	6.00	0.0000	Actual

Table 7: Confirmation

Response	Predicted mean	Predicted median	Std Dev	n	SE Pred	95% PI low	95% PI high
DT	20.3922	20.3922	2.43427	1	2.5659	14.1136	26.6709
Tensile	0.0056333	0.0056333	0.0011498	1	0.0012120	0.0026674	0.00085991
	3	3	8	1	8	8	8
DR	102.182	102.182	14.4031	1	15.1823	65.0326	139.332

Two-sided Confidence = 95%

Formulation code	Factor-1: HPMCE52v (mg)	Factor-2: PEG400 (ml)	Respnse-1: DT (sec)	Response-2: tensile strength (N/mm²)	Response-3: %CDR
F1	100	2	23.63	0.0053	94.2
F2	150	4	23.9	0.0068	128
F3	200	6	20.6	0.0054	98.5
F4	100	2	16.53	0.0055	126.4
F5	150	4	20.77	0.0046	95.25
F6	200	6	24.23	0.0066	96.74
F7	100	2	16.77	0.0071	98.8
F8	150	4	16.4	0.0041	89.25
F9	200	6	20.77	0.0053	95.25

Drug polymer compatibility

FT-IR

To investigate any possible interactions between drug and the utilized polymer under investigation FT-IR spectrophotometer method was used. The IR spectra of pure drug (Dipyridamole) and its physical mixture were carried out by the FT-IR spectrophotometer (fig. 6 and 7).

A sharp and decrease in altered of peak at 1627.63 cm^{-1}, a peak between 1615-1495 and at 612.39 cm^{-1}, represents a double bond and the overlapping of functional groups of aliphatic and aromatic compounds. A strong band occurred at 2919.7 cm^{-1} as a result of sulphides of keratin molecules (fig. 7). Thus, the FTIR analysis revealed the compatibility between the components of the DPI with mere association and/or conjugation of their groups. The studied effect might be possible to connect all the components together in order to form a continuous scaffold.

Scanning electron microscopy (SEM)

Scanning electron microscopy (SEM) was used to investigate the morphology of crystal formations. Samples were mounted on aluminum pin stubs using self-adhesive carbon mounts (Agar Scientific, Stansted, UK). A FEI Quanta 400 scanning electron microscope was used to take SEM pictures of the mounted samples (fig. 8).

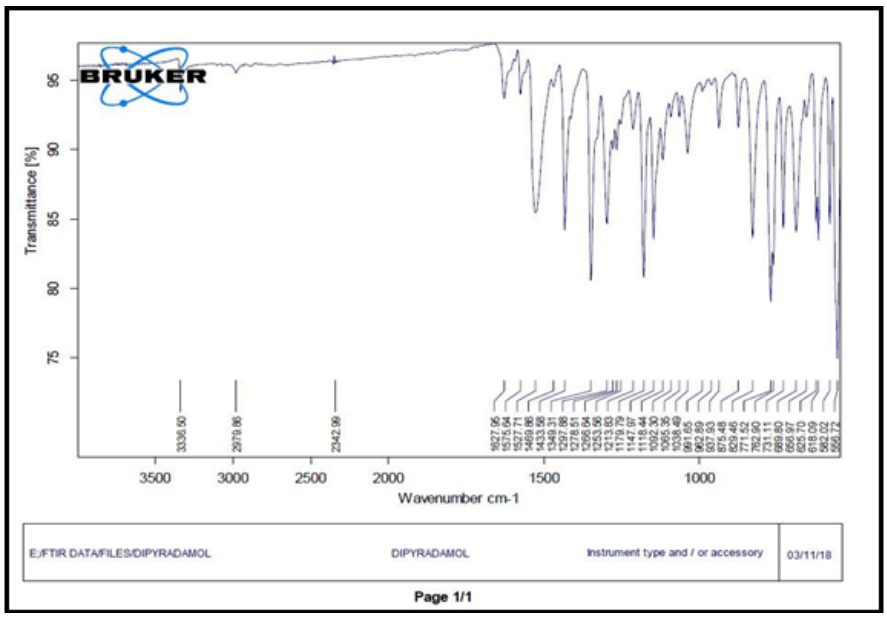


Fig. 6: FT-IR spectrum of dipyridamole pure drug

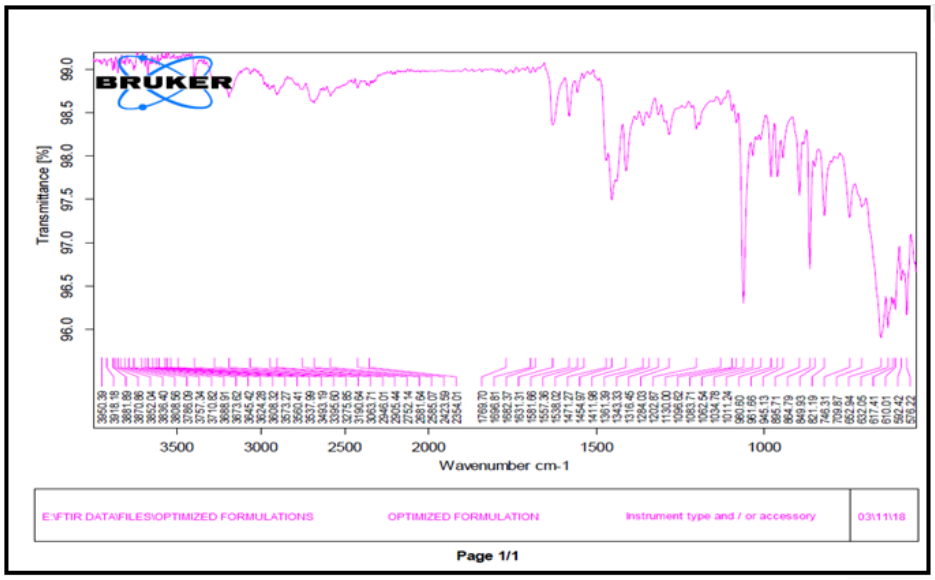


Fig. 7: FT-IR spectrum of dipyridamole optimized formulation

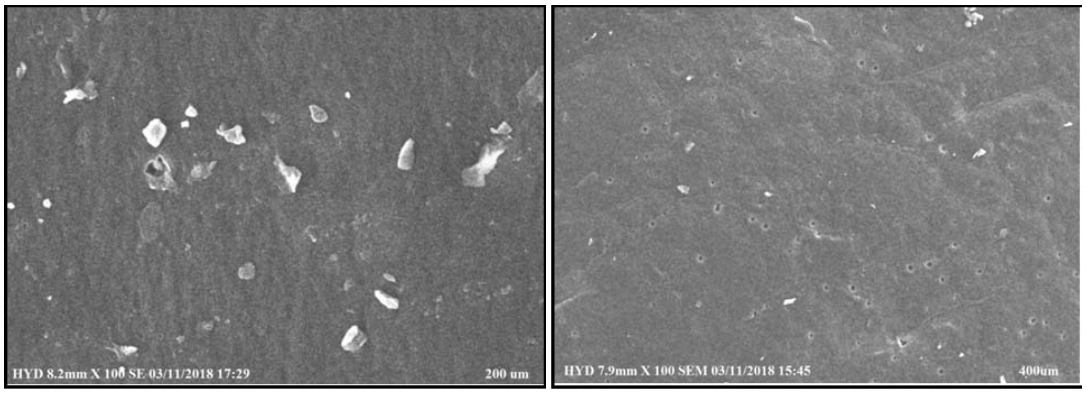


Fig. 8: SEM of dipyridamole optimized formulation at 200 µm and 400 µm

Differential scanning calorimetry (DSC)

DSC Q2000 from TA instruments was used for FI and FII. Under a nitrogen environment, 2-4 mg of the sample were heated in a sealed standard aluminum pan from 25 to 200 C at a heating rate of 100C/min. The TA Universal analysis 2000 program was used to examine the DSC data. (fig. 9 and fig. 10).

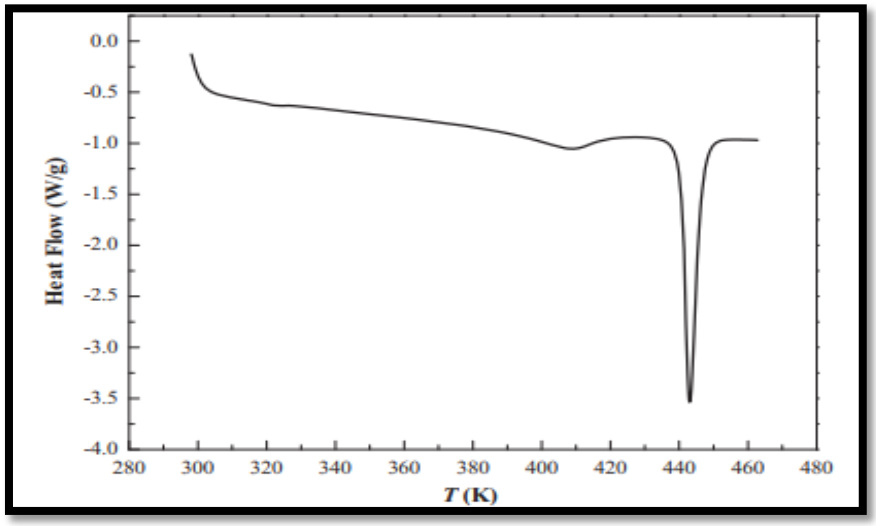


Fig. 9: DSC thermogram of DPI

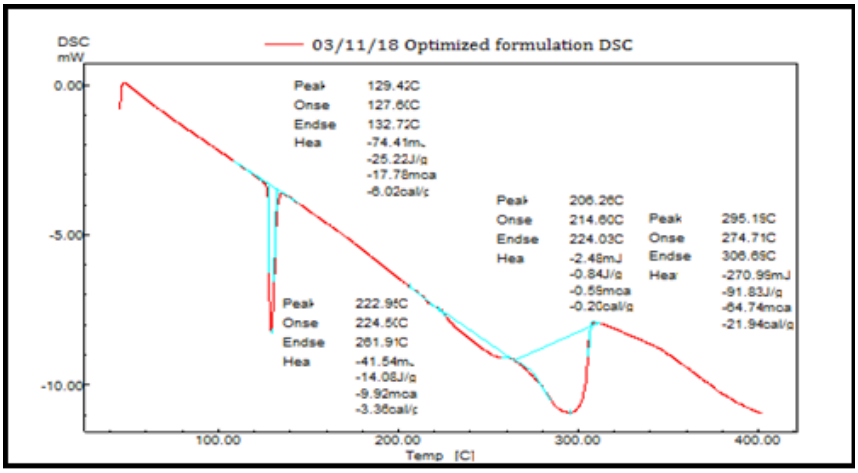


Fig. 10: DSC of dipyridamole optimized formulation

CONCLUSION

Dipyridamole oral rapid soluble oro-dispersable films were prepared successfully by using Solvent casting method with the following polymers: HPMC $E_5$2v and plasticizer PEG (400). The prepared formulations were evaluated for Content uniformity, Weight variation, Thickness, Percent elongation, Tensile strength, *In vitro* time of disintegration and percent drug released. Among all formulations films prepared using HPMC $E_5$2v and plasticizer, PEG 400 showed best results. Oral rapid soluble orodispersable films would be a promising oral delivery system. Oral thin films directly placed below the tongue it is easily dissolved or disintegrated and it shows the fast action. It is mainly useful for the children who are unable to take tablet or capsules. It is concluded that oral thin film of Dipyridamole having more bioavailability and rapid onset of action and it avoids the fast pause effect.

ACKNOWLEDGEMENT

I would like to express my special thankful to the management of Nizam Institutions of Pharmacy, Deshmukhi, Hyderabad, India, for supporting in completing the research successfully.

FUNDING

Nil

AUTHORS CONTRIBUTIONS

NA.

CONFLICT OF INTERESTS

Declared none

REFERENCES

1. Alqahtani A, Raut B, Khan S, Mohamed JMM, Fatease AA, Alqahtani T. The unique carboxymethyl fenugreek gum gel loaded itraconazole self-emulsifying nanovesicles for topical onychomycosis treatment. Polymers (Basel). 2022 Jan 14;14(2):325. doi: 10.3390/polym14020325, PMID 35054731, PMCID PMC8779379.
2. Price TM, Blauer KL, Hansen M, Stanczyk F, Lobo R, Bates GW. Single-dose pharmacokinetics of sublingual versus oral administration of micronized 17 beta-estradiol. Obstet Gynecol. 1997 Mar;89(3):340-5. doi: 10.1016/S0029-7844(96)00513-3, PMID 9052581.
3. Walton RP. Absorption of drugs through the oral mucosa. III. Fat-water solubility coefficient of alkaloids. Experimental Biology and Medicine. 1935;32(9):1488-92. doi: 10.3181/00379727-32-8147C.
4. Kurosaki Y, Takatori T, Nishimura H, Nakayama T, Kimura T. Regional variation in oral mucosal drug absorption: permeability and degree of keratinization in hamster oral cavity. Pharm Res. 1991 Oct;8(10):1297-301. doi: 10.1023/a:1015812114843. PMID 1724562.
5. Ghosh TK, Pfister WR. Quick dissolving oral dosage forms: scientific and regulatory considerations from a clinical pharmacology and biopharmaceuticals perspective. Drug Delivery to the Oral Cavity: Molecules to Market. Boca Raton: CRC Press; 2005. p. 337-56.
6. Mohamed JMM, Alqahtani A, Kumar TVA, Fatease AA, Alqahtani T, Krishnaraju V. Superfast synthesis of stabilized silver nanoparticles using aqueous allium sativum (Garlic) extract and isoniazid hydrazide conjugates: molecular docking and *in vitro* characterizations. Molecules. 2021 Dec 24;27(1):110. doi: 10.3390/molecules27010110, PMID 35011342, PMCID PMC8746848.
7. Wang Q, Sivakumar K, Mohanasundaram S. Impacts of extrusion processing on food nutritional components. Int J Syst Assur Eng Manag. 2022;13(S1):364-74. doi: 10.1007/s13198-021-01422-2.
8. Ramakrishna N, Mishra B. Plasticizer effect and comparative evaluation of cellulose acetate and ethylcellulose-HPMC combination coatings as semipermeable membranes for oral osmotic pumps of naproxen sodium. Drug Dev Ind Pharm. 2002 Apr;28(4):403-12. doi: 10.1081/ddc-120003001, PMID 12056533.
9. Roy A, Ghosh A, Datta S, Das S, Mohanraj P, Deb J. Effects of plasticizers and surfactants on the film-forming properties of hydroxypropyl methylcellulose for the coating of diclofenac sodium tablets. Saudi Pharm J. 2009 Jul;17(3):233-41. doi: 10.1016/j.jsps.2009.08.004. PMID 23964166, PMCID PMC3731028.
10. Mohamed JMM, Alqahtani A, Ahmad F, Krishnaraju V, Kalpana K. Stoichiometrically governed curcumin solid dispersion and its cytotoxic evaluation on colorectal adenocarcinoma cells. Drug Des Dev Ther. 2020 Nov 2;14:4639-58. doi: 10.2147/DDDT.S273322. PMID 33173275, PMCID PMC7648666.
11. Mohamed JMM, Alqahtani A, Khan BA, Al Fatease A, Alqahtani T, Venkatesan K. Preparation of a soluble complex of curcumin for the potential antagonistic effects on human colorectal adenocarcinoma cells. Pharmaceuticals (Basel). 2021 Sep 19;14(9):939. doi: 10.3390/ph14090939, PMID 34577638, PMCID PMC8467777.
12. Mohanasundaram S, Doss VA, Maddisetty P, Magesh R, Sivakumar K, Subathra M. Pharmacological analysis of hydroethanolic extract of Senna alata (L.) for *in vitro* free radical scavenging and cytotoxic activities against Hep G2 cancer cell line. Pak J Pharm Sci. 2019;32(3):931-4.
13. Mohamed JMM, Alqahtani A, Al Fatease A, Alqahtani T, Khan BA, Ashmitha B. Human hair keratin composite scaffold: characterisation and biocompatibility study on NIH 3T3 fibroblast cells. Pharmaceuticals (Basel). 2021 Aug

9;14(8):781. doi: 10.3390/ph14080781, PMID 34451878, PMCID PMC8401710.
14. Nagadeep J, Kamaraj P, Arthanareeswari M. Gradient RP-HPLC method for the determination of potential impurities in dabigatran etexilate in bulk drug and capsule formulations. Arab J Chem. 2019;12(8):3431-43. doi: 10.1016/j.arabjc.2015.09.006.
15. Nagadeep J, Kamaraj P, Arthanareeswari M. Enantiometric separation of sitagliptin in a fixed-dose combination formula of sitagliptin and metformin by a chiral liquid chromatographic method. Int J Pharm Pharm Sci. 2019;11(6):66-71.
16. Jaishetty N, Palanisamy K, Maruthapillai A, Jaishetty R. Trace Level Quantification of the (-)2-(2-amino-5-chlorophenyl)-4-cyclopropyl-1,1,1-trifluoro-3-butyn-2-ol genotoxic impurity in efavirenz drug substance and drug product using LC-MS/MS. Sci Pharm. 2015;84(3):456-66. doi: 10.3390/scipharm84030456. PMID 28117312.
17. Janakiraman AK, Sumathi B, Saleem TM, Ramkanth S, Kumar PO, Venkatachalam G. Design and evaluation of carvedilol nanocrystals sustained-release tablets. J Appl Pharm Sci. 2017;7(4):61-8.
18. Doss VA, Mohanasundaram S, Maddisetty P. Analysis of hydroethanolic extract of Senna alata (L.) to screen bioactive compounds with inhibitory activity on lipid peroxidation, *in vitro* antibacterial and antidiabetic efficacy. Int J Pharm Sci. 2016;6(1):1360-6.
19. Mohamed JMM, Alqahtani A, Ahmad F, Krishnaraju V, Kalpana K. Stoichiometrically governed curcumin solid dispersion and its cytotoxic evaluation on colorectal adenocarcinoma cells. Drug Des Dev Ther. 2020 Nov 2;14:4639-58. doi: 10.2147/DDDT.S273322. PMID 33173275, PMCID PMC7648666.
20. Irfan M, Rabel S, Bukhtar Q, Qadir MI, Jabeen F, Khan A. Orally disintegrating films: a modern expansion in drug delivery system. Saudi Pharm J. 2016 Sep;24(5):537-46. doi: 10.1016/j.jsps.2015.02.024. PMID 27752225, PMCID PMC5059831.
21. Rangarajan N, Sangeetha R, Mohanasundaram S, Sampath, Porkodi K, Dass Prakash MV. Additive inhibitory effect of the peels of Citrus limon and Citrus sinensis against amylase and glucosidase activity. IJRPS 2021;11(4):6876-80. doi: 10.26452/ijrps.v11i4.3661.
22. Patel RS, Poddar SS. Development and characterization of mucoadhesive buccal patches of salbutamol sulphate. Curr Drug Deliv. 2009;6(1):140-4. doi: 10.2174/156720109787048177, PMID 19418966.
23. Mohanasundaram S, Doss VA, Haripriya G, Varsha M, Daniya S, Madhankumar. GC-MS analysis of bioactive compounds and comparative antibacterial potentials of aqueous, ethanolic and hydroethanolic extracts of Senna alata L. against enteric pathogens. Int J Res Pharm Sci. 2017;8(1):22-7.
24. Nagaraju T, Gowthami R, Rajashekar M, Sandeep S, Mallesham M, Sathish D. Comprehensive review on oral disintegrating films. Curr Drug Deliv. 2013 Feb;10(1):96-108. doi: 10.2174/1567201811310010016, PMID 22920576.
25. Jamal Moideen MM, Alqahtani A, Venkatesan K, Ahmad F, Krisharaju K, Gayasuddin M. Application of the box-behnken design for the production of soluble curcumin: skimmed milk powder inclusion complex for improving the treatment of colorectal cancer. Food Sci Nutr. 2020 Oct 30;8(12):6643-59. doi: 10.1002/fsn3.1957, PMID 33312548, PMCID PMC7723192.
26. Mohamed JM, Alqahtani A, Ahmad F, Krishnaraju V, Kalpana K. Pectin co-functionalized dual-layered solid lipid nanoparticle made by soluble curcumin for the targeted potential treatment of colorectal cancer. Carbohydr Polym. 2021 Jan 15;252:117180. doi: 10.1016/j.carbpol.2020.117180. PMID 33183627.