ORODISPERSIBLE FILM FABRICATION BY HOT MELT EXTRUSION FOR DENTAL PAIN AMELIORATION BY QUALITY BY DESIGN APPROACH

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(Received 11 May 2022) (Accepted 16 February 2023)

ABSTRACT

Surgical dental procedures cause pain and inflammation leading to temporary restriction of the movement of the oral cavity. Consumption of analgesic medications in the form of tablets or dispersible tablets causes compliance issues due to the compromised movability of the mandibular joint. An Orally Disintegrating Film (ODF), due to its pliability and compact size, can be a patient compliant tool for management of postoperative dental pain over parenterally administered opioids, conventional as well as orodispersible tablets of steroids or NSAIDS. Due to the inadequacies involved in solvent-casting, an unmet need exists for a continuous, eco-friendly and patient compliant process of manufacturing. The present research work addresses the unmet need of a patient compliant delivery system containing ketorolac tromethamine by Hot Melt Extrusion. The ODF optimized by Quality by Design was found to be stable with excellent mechanical properties and provided superior release profile as compared to the equivalent marketed formulation.

Keywords: Orally disintegrating films (ODFs), Hot melt extrusion (HME), Ketorolac tromethamine (KT), QbD, DoE, Pain management

INTRODUCTION

Dental pain is an inevitable outcome of oral health issues and the related surgical procedures. It is often neglected as inconsequential in the beginning but causes extreme inflammation and discomfort with progression. The prevalence of dental pain associated with oral health issues is 33% in the pediatric population, followed by 25% in the adult population[1].

The financial burden imposed by the treatment is seldom affordable to every stratum of society. The direct expenditure associated with oral health care claims 4.6% of the global health budget[2]. The treatments in case of chronic oral health problems generally involve surgical interventions like root canals, cavity fillings, molar extractions and wisdom tooth extractions. These procedures are invasive and lead to severe inflammation and pain for a significant duration even after the surgery. Apart from the pain, the inflammation interferes with normal activities like chewing, biting, swallowing, speaking and laughing. The effects are long lasting and interfere with quality of life of the affected individual[1]. Thus, managing the post operative pain and inflammation is a serious challenge.

The current treatment regime employs opioids, NSAIDs and steroids to alleviate the pain and oedema associated with dental procedures. Use of opioids and steroids has its own limitations due to the severity of side effects associated with them. These medications are either given orally or, in some cases, parenterally. Parenteral administration causes pain. Amongst the oral formulations, immediate release tablets offer quick relief but oral administration is difficult as movement of the mandibular joint is compromised due to severe inflammation.

There is an unmet need to provide an efficient delivery system with NSAIDs that will offer equivalent symptomatic relief from pain and inflammation without straining the mandibular joint and causing serious secondary implications like addiction or steroid induced complications.

The research in the field of pain management is rising over the years owing to the requirement for delivery systems curated to address the diverse set of demands

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https://doi.org/10.53879/id.60.07.13501

in the management of different type of pain i.e., acute, chronic, sub chronic, etc.[3]

Ketorolac tromethamine (KT) is a NSAID with analgesic activity comparable to some opioids. It is primarily used to treat dental pain[4]. The adverse effects associated with the opioids can be avoided by KT without compromising on the therapeutic efficacy, thereby making KT a choice of alternative to opioids in the management of moderate to severe pain[5] . Marketed formulations of KT include only conventional tablets, injectables and solutions[6].

Generally, severe inflammation is associated with dental procedures like root canal or tooth removal[7]. The inflammation can make it difficult for the patients to open their mouth sufficiently for administration of a conventional tablet. In such cases, an ODF can be a real help given its flexibility and minute thickness. Even when compared to an orodispersible tablet (ODT), an ODF is a more compact and convenient dosage form. It will offer quick pain relief with enhanced patient compliance. No ODF is presently available for KT in the market. ODF would provide quick relief from pain without straining the mandibular joint. Additionally, it offers ease of transportation and storage over ODTs. An additional scope for extension of patent life is another significant feature of ODF[8,9].

ODFs are commercially prepared by solvent-casting method. It is a non-continuous batch process for manufacturing of films. Presence of organic solvents calls for an additional gas chromatography- mass spectroscopic analysis to check the residual solvents. Hot melt extrusion (HME) has proved to be an efficient and green technique for manufacturing pharmaceutical dosage forms. HME technology is a one-step, continuous and solvent-free process applicable to the manufacturing of varied pharmaceutical dosage forms e.g., tablets, pellets, granules, implants, inserts, suppositories, ointments, gels and films.

The application of HME technology in the formulation of films has shown promising results[10]. It is an industrially feasible, continuous, and scalable technique for the production of orodispersible films. It offers the advantages like fewer unit operations, continuous and solvent-free manufacturing, enhanced uniformity in drug distribution and better stability[8]. The technology subjects the drug-excipients blend to temperature and sheer energy and extrudes it through a die having the dimensions of the desired dosage form.

HME is an efficacious alternative to the conventional technique i.e., solvent-casting, as it reduces the intrinsic limitations of solvent-casting. HME offers a greener and continuous process which is industrially scalable with few unit operations and enhanced content uniformity for the manufacturing process of ODFs[11,12]. Hot melt extruded ODF of KT will prove to be a patient compliant, green and cost-efficient manufacturing process.

Application of the said technology for the development of an eco-friendly, patient compliant delivery system which not only targets patient compliance but also offers simpler, scalable method of manufacturing with fewer unit operations will address the unmet need in the management of dental pain.

MATERIALS AND METHODS

Materials

Ketorol-DT was sourced from MSN Pharma, Hyderabad. Soluplus® was a gift from BASF. The lemon flavour was sourced from Givaudan, India. Citric acid was purchased from SDFCL. Glycerin IP was purchased from VVF India Limited, sucralose was bought from Gangawal Chemicals, India and Sodium starch glycolate (SSG) from Prachin Chemicals, India.

Methods

Hot melt extrusion

Trials were conducted on a twin screw counter-rotating HME (Thermoscientific, HAAKE MiniCTW). The solid ingredients were blended for 10 minutes at 10 RPM in a V-cone blender. The plasticizer was then added to the mixture and blended manually for 10 minutes[13]. The resulting blend was fed to the hopper and extruded through a 10 mm*0.2 mm die. The primary trials were conducted over 25-75 rpm and a temperature of 100-125 °C. The films were sliced into unit dosage form. Each film was sealed and stored in aluminum pouches[14].

Application of QbD and DoE approach

DoE was used to evaluate the inter-relevance between independent variables and dependent responses[15,16]. The Box-Behnken Design (BBD) is a statistical optimization design employed to study the influence of the independent variables on the quality of the product[17,18]. The layout of the BBD is presented in Table I. Disintegration time, drug release and folding endurance were chosen as the dependent variables. The independent variables such as polymer concentration, disintegrant concentration and concentration of the plasticizer were optimized with the assistance of the software to obtain desired values of the dependent responses.

Physicochemical characterization

Film thickness

The thickness of the ODF was gauged in triplicate and the average has been reported[19,20].

Weight variations

The samples taken at random from different parts of the ODF (center, both the ends) were weighed individually (n=3) and the average has been reported.

Surface pH of the film

The film was wetted with 5 µL water and pH was measured (n=6). The samples were removed at random from the ends and center part to represent the extruded film thread. The mean pH was noted.

Moisture content

ODF sample was kept in the moisture balance and heated at 105 ºC till a constant reading was recorded. The samples were taken at random from different parts of the extruded film thread (parts near the ends and center) to span the length of the thread. The mean value (n=3) has been reported.

Disintegration test

The samples taken at random from the ends and center were subjected to 20 mL phosphate buffer (pH 6.8) in a petri plate. The time required for disintegration was noted at 25 °C (n =3) [21,22].

Folding endurance

Folding endurance is calculated by folding the film at an angle of 180 ° at the same spot till it breaks. The mean folding endurance of samples taken at random from different parts of the film was noted[20].

Texture analysis

CT3 texture analyzer was used to evaluate the texture of the optimized film. TA15/1000 Tensile probe and TA-DGA fixture and a load cell of 10 kg was used for the testing. The rectangular film specimens (5 mm*80 mm *0.2 mm) was longitudinally placed in the tensile grip probe. The ODFs were held between a

Table I: Layout of Box–Behnken optimization experimental design

Independent variables	Levels		
	Low	**Medium**	**High**
		Coded Values	
	-1	**0**	**+1**
A= Concentration of Soluplus® (% w/w)	45.00	50.00	55.00
B= Concentration of Glycerin (% w/w)	5.00	7.50	10.00
C= Concentration of SSG (% w/w)	5.00	10.00	15.00

Dependent variables/ Responses

R1= Disintegration Time (Second)

R2= Folding Endurance (-)

R3= Percent cumulative drug release at 30 min (%)

Table II: Box–Behnken optimization design with responses

Std.	A: Concentration of Soluplus®	B: Concentration of Glycerol	C:Concentration of SSG	Disintegration Time	Folding Endurance	Release at 30 Minutes
	%	%	%	Sec	-	%
1	50	10	15	33	2	100
2	45	7.5	15	44	4	100
3	50	7.5	10	39	25	100
4	45	10	10	51	3	100
5	50	7.5	10	38	25	99.7
6	50	7.5	10	40	25	99.7
7	50	7.5	10	39	24	99.3
8	50	7.5	10	39	24	99.1
9	50	5	15	43	1	98.2
10	45	7.5	5	55	3	98
11	45	5	10	53	3	97.6
12	50	10	5	47	3	97
13	55	7.5	15	45	4	93.8
14	50	5	5	55	1	93
15	55	10	10	48	4	91.1
16	55	7.5	5	58	2	88.5
17	55	5	10	62	2	87

Table III: Summary of ANOVA results for the dependent variables

ANOVA parameter	R_1 : Disintegration time	R_2 : Folding endurance	R_3:Release at 30 minutes
R^2	0.9967	0.9980	0.9916
Adjusted R^2	0.9925	0.9954	0.9807
Predicted R^2	0.9746	0.9779	0.8900
Standard deviation	0.7071	0.7020	0.5952
Adequate Precision	52.5514	44.5269	28.5344
Model F-value	236.58	385.13	91.29
Model p-Value	<0.0001	<0.0001	<0.0001

pair of clamps situated 5 mm apart and a crosshead speed of 2.5 mm s^{-1} was employed for the testing. The tensile strength (Ts) was computed using the texture analysis result[14].

In vitro dissolution studies

The *in vitro* dissolution study was carried out in 30 mL artificial saliva medium (pH 6.8) at 100 RPM for 30 minutes[14]. In addition, *in vitro* release study was conducted (n=3) for a marketed immediate release dispersible tablet, Ketorol DT containing 10 mg KT. The release study for the ODT was carried out in USP type 2 apparatus in pH 6.8 phosphate buffer.

Drug content (%)

Drug content was checked by UV spectrophotometry. The specimens (n=3) were individually dissolved in buffer (pH 6.8, 50mL) and subsequently diluted to determine the content of KT in ODF by comparing it to the theoretical content.

Scanning electron microscopy

The SEM of the final ODF was performed to evaluate the surface topology[14].

RESULTS

Application of QbD and DoE approach to KT ODF

The effects of concentration of Soluplus® (A), glycerin (B) and SSG (C) upon disintegration time (R1), folding endurance (R2) and release of KT at 30 min (R3) were evaluated by QbD approach. The results of the suggested 17 trials were statistically analyzed by the software Design Expert®, version thirteen. The trials with responses are summarized in Table II.

The summary of ANOVA results is shown in Table III.

The best-fitted statistical model for all the responses was the quadratic model.

The polynomial quadratic equations were analyzed for magnitude and coefficients of mathematical signs The higher the magnitude of the coefficient, greater is the impact of formulation variable on the dependent response. A positive sign of coefficient suggests a direct proportionality, whereas a negative sign reflects inverse proportionality with the selected response. The main effects (X1, X2, and X3) reveal the response to changing one factor at a time from low to high level. The interaction terms (X12, X23, and X13) depict the change in the dependent variable in response to simultaneous change in the values of two independent variables. The polynomial quadratic terms (X11, X22, and X33) were employed to assess nonlinearity.

Effect of formulation parameters on the dependent responses

Disintegration time (R1)

The *in vitro* disintegration time of the ODFs ranged from 33-62 seconds. The values are noted in Table II.

Disintegration time for the optimized ODF was 40.33± 0.57 s which is in agreement with the predicted value i.e., 40.920 seconds (Table IV).

The polynomial quadratic equation for (*R1*) is presented as

$$R1 = 39 + 1.25A - 4.25B - 6.25C - 3AB - 0.5BC - 0.5AC + 10.25A^2 + 4.25B^2 + 1.25C^2 \quad \text{..... (1)}$$

Folding endurance (R2)

Folding endurance of the melt extruded films ranged between 1 to 25. The values are mentioned in Table II.

The optimized ODF was flexible with adequate mechanical strength. The folding endurance of optimized ODF was 24.33 ±0.47 which is in agreement with the predicted value 22.295 (Table IV). It can withstand packaging and transportation.

The polynomial quadratic equation for (*R2*) is presented as

$$R2 = 24.6 - 0.125A + 0.625B + 0.25C + 0.25AB - 0.25BC + 0.25AC - 10.05A^2 - 11.55B^2 - 11.3C^2 \quad \text{..... (2)}$$

Release at 30 minutes (R3)

The criteria for immediate release solid oral dosage forms with highly water-soluble drugs is $Q_{80\%}$ in 30 minutes. KT, a BCS class I drug, falls in the category of high solubility drugs. The target was to attain complete release in 30 minutes. The release at the end of 30 minutes for all the films is reported in Table II.

The *in vitro* release for the software predicted batch was 100% at the end of 30 minutes, which is in agreement with the suggested value i.e., 100.365% (Table IV).

The polynomial quadratic equation for (*R3*) is presented as

Table IV: Composition of the optimized ODF with predicted and observed responses

Formulation variable	A: Concentration of Soluplus®	B: Concentration of glycerin	C: Concentration of SSG
Levels	48% w/w	7.00 % w/w	15% w/w
Responses	R1: Disintegration time	R2: Folding endurance	R3: Percent cumulative drug release at 30 min (%)
Predicted values	40.920 s	22.295	100.365
Observed values	40.33± 0.57 s	24.33±0.47	100
Percent validity of model (%)	99.80	95.42	99.64

Table V: Optimized formula with characterization

Ingredient	Quantity %	Thickness	0.20±0.07 mm
Ketorolac tromethamine	10	**Surface pH**	5.85±0.012
Soluplus®	48	**Moisture content**	0.22 ±0.68 %
Glycerin	07	**Drug content**	100.30±0.002 %
Sodium starch glycolate	15	**Disintegration time**	40.33± 0.57 s
Citric acid	10	**Folding endurance**	24.33 ±0.47
Sucralose	05	**Tensile strength**	42.166±0.88 Ncm^{-1}
Orange flavor	05	**Release at 30 minutes**	100.06±0.09 %

R3 = 99.56-4.4A +1.5375B + 1.9375C +0.425AB – 0.55BC +0.825AC – 3.805A^2-1.83B^2 0.68C^2 .....(iii)

3-Dimensional response surface analysis

The 3D plots provide a distinct graphical visualization of the impact of the variables on the dependent responses. The graphical representation of 3D plots is summarized in Figs. 1, 2 and 3.

Identification of optimum values of formulation variables

QbD was applied to the present research work to ascertain the critical formulation parameters and determine the optimum values of those parameters to attain the desired values in terms of the dependent variables. The design space quantified by the overlay plots was use to achieve the anticipated formulation goals.

ODFs loaded with KT were optimized for disintegration time, folding endurance and drug release at 30 minutes based on the impact of formulation variables, concentration of Soluplus®, concentration of glycerin and concentration of SSG. The considerations from the polynomial equations, 2D and 3D graphs and overlay plots to identify the design space with suggested optimized solutions with highest desirability. Out of the solutions offered by the software, one with unit desirability was selected. The optimized formulation containing 48 % Soluplus®, 7 % glycerin and 10 % SSG was formulated and analyzed successfully. The details about the same and the percent validity of the statistical model are incorporated in Table IV. The composition and characterization of the optimized product is summarized in Table V.

The congruence of the predicted and observed values of the dependent responses (Table IV) confirmed the validity of the statistical model. The model was found to be reliable to predict the dependent responses. The optimized formula was taken for further physicochemical characterization.

Physicochemical characterization

The ODF containing 10 % w/w KT was formulated by HME with Soluplus®, glycerin and sodium starch glycolate as the choice of polymer, plasticizer and disintegrant, respectively.

The batches suggested by the software were carried out at 125 ℃ and 75 RPM.

Values of film thickness, weight variation, moisture content, drug content are listed in Table VI. Values of surface pH and tensile strength are incorporated in Table IV with the characteristics of the optimized formulation.

In vitro dissolution

The *in vitro* release profiles of all the films are graphically represented in Fig. 4 with release profile of marketed formulation, Ketorol-DT. The latter showed only 81.233 % release at the end of 30 minutes.

The release at the end of 30 minutes for all the films is summarized in Table II.

The *in vitro* release at the end of 30 minutes for the software predicted batch was 100 %, which is in agreement with the proposed value i.e., 100.365 % (Table IV).

Scanning electron microscopy

The SEM images of the film surface (Fig. 5) indicate that the film surface is fairly uniform.

Table VI: Characterization of melt extruded films

Formulation code	Thickness (mm)	Weight (mg)	Moisture content (%)	Drug content (%)
F1	0.20±0.03	100.1±0.17	0.33±0.01	102.93±0.001
F2	0.20±0.02	101.33±1.52	0.27±0.02	101.06±0.001
F3	0.21±0.05	101.17±1.04	0.33±0.003	99.24±0.03
F4	0.24±0.03	100.17±0.76	0.41±0.01	99.59±0.01
F5	0.20±0.01	99.47±0.55	0.39±0.01	99.59±0.04
F6	0.22±0.07	100.43±0.75	0.35±0.002	99.03±0.004
F7	0.21±0.02	100.33±0.98	0.23±0.01	100.91±0.003
F8	0.21±0.05	99.8±1.31	0.36±0.004	101.31±0.05
F9	0.22±0.01	100.1±0.458258	0.334±0.01	100.30±0.0.02
F10	0.20±0.02	100.4±0.53	0.41±0.003	101.11±0.004
F11	0.21±0.01	101.67±0.29	0.36±0.003	99.94±0.002
F12	0.20±0.03	101.33±1.04	0.27±0.01	100.15±0.003
F13	0.22±0.04	99.97±0.45	0.26±0.01	100.45±0.0.05
F14	0.25±0.03	100.4±0.69	0.35± 0.01	99.29±0.03
F15	0.22±0.04	99.8±0.2	0.32±0.01	100.25±0.003
F16	0.24±0.02	100.7±1.04	0.234±0.005	101.87±0.002
F17	0.22±0.05	99.77±0.21	0.26±0.02	99.24±1.05
Optimized Batch	0.2±0.01	100.27±0.25	0.28±0.0002	100.30±0.002

DISCUSSION

Disintegration time

Disintegration time of the ODF is an extremely important criterion in assessment of its performance as quick disintegration is prerequisite for quick release of KT for immediate analgesic action.

It is evident from the equation (1) that the factor A, i.e., concentration of the Soluplus® has a positive impact on the disintegration time. Concentration of glycerin and SSG exert a negative impact. The stagnant layer formation by Soluplus® around KT could have led to decrease in the rate of disintegration. Concentration of glycerin, in contrast, has a negative coefficient. It reduces the disintegration time. The elasticity imparted by glycerin alleviates the strength of the stagnant layer by Soluplus® which causes rapid disintegration. Disintegrating agent, in consequence, aids disintegration and hence has a negative coefficient. Magnitudes of the main effects, interaction terms and quadratic terms suggest that concentration of Soluplus® is the most crucial factor in determination of the disintegration time followed by concentration of the disintegrant.

Folding endurance

Folding endurance is a marker of plasticity and mechanical strength of a film. As the equation (2) clarifies, folding endurance is prominently regulated by the interaction of factors quadratic terms over the main effects in isolation. The magnitudes of terms A^2, B^2, C^2 are maximum. Presence of Soluplus® reduces the folding endurance, whereas plasticizer and disintegrant produce a mixed effect as the signs of coefficients of the main effects differ from those of the interaction terms and quadratic

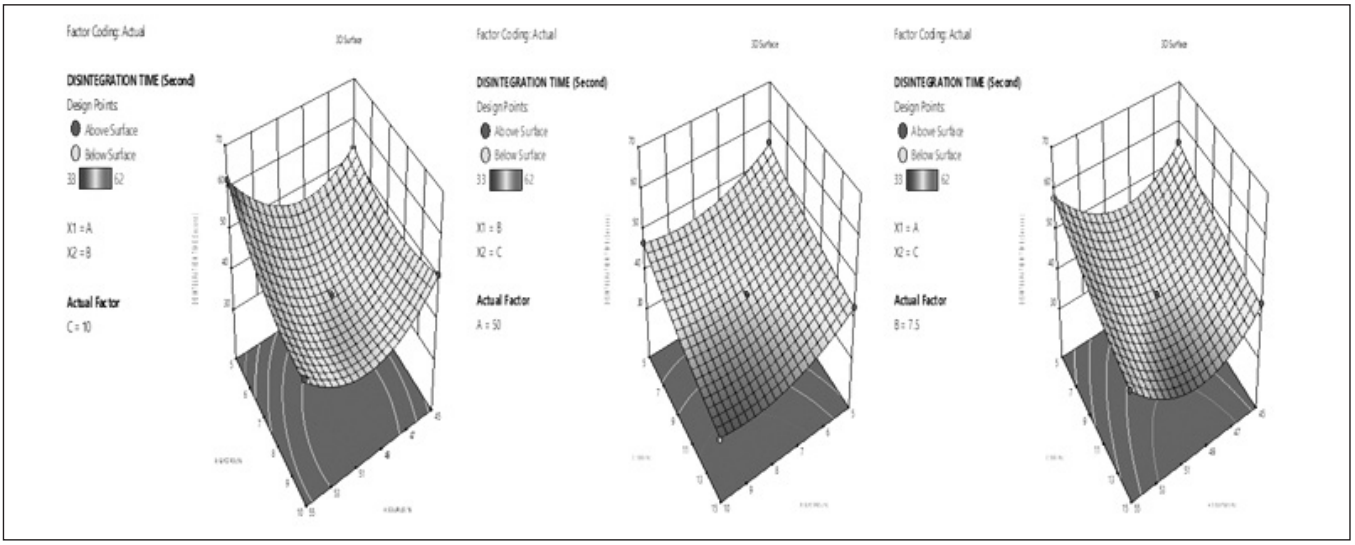

Fig. 1: 3D plot of effect on disintegration time

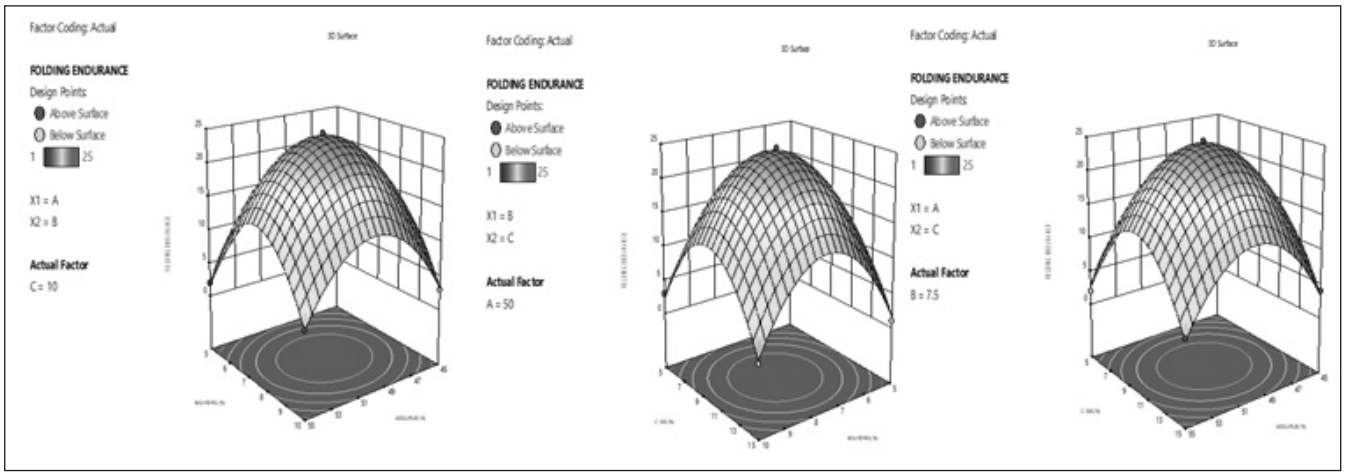

Fig. 2: 3D plot of effect on folding endurance

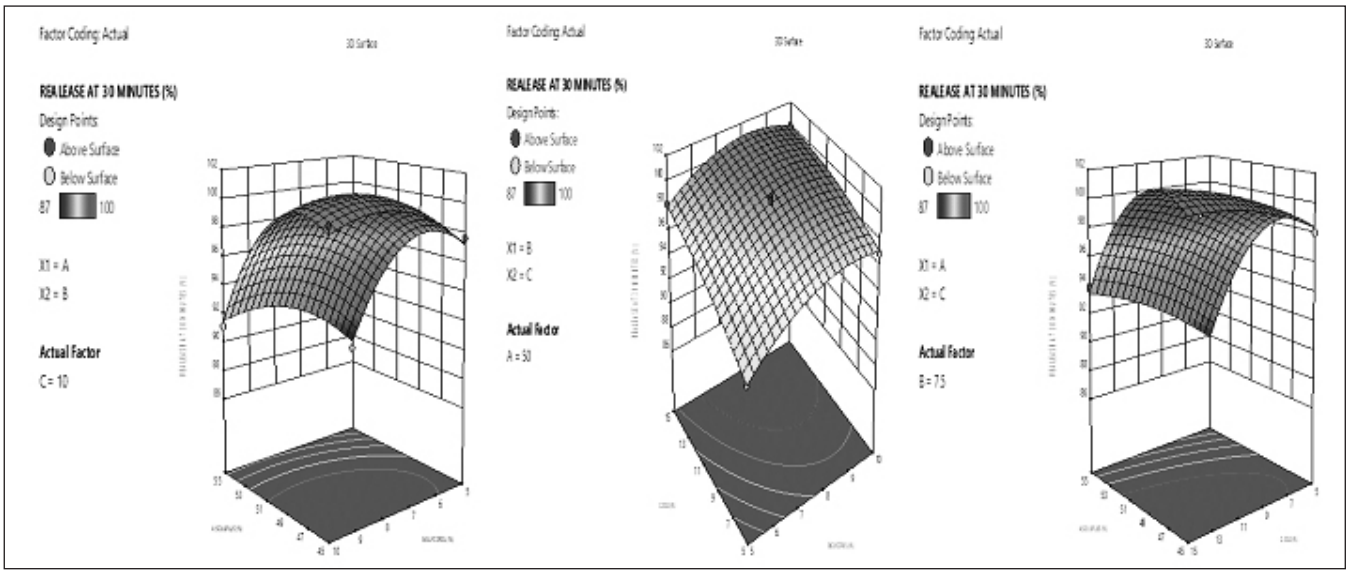

Fig. 3: 3D plot of effect on release at 30 minutes

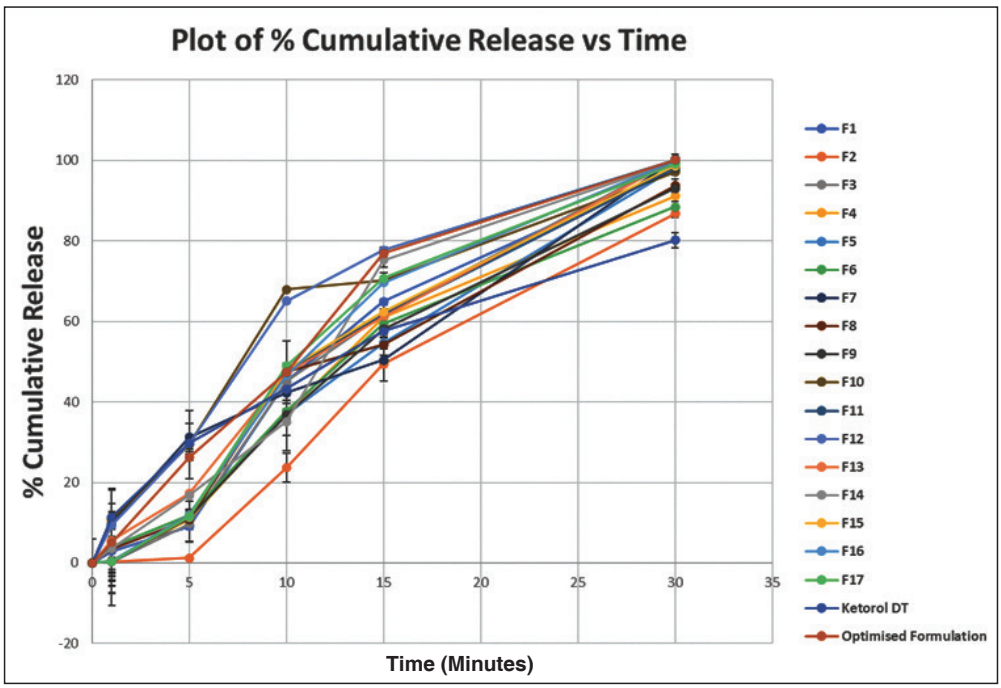

Fig. 4: *In vitro* release profile of ODFs and marketed formulation

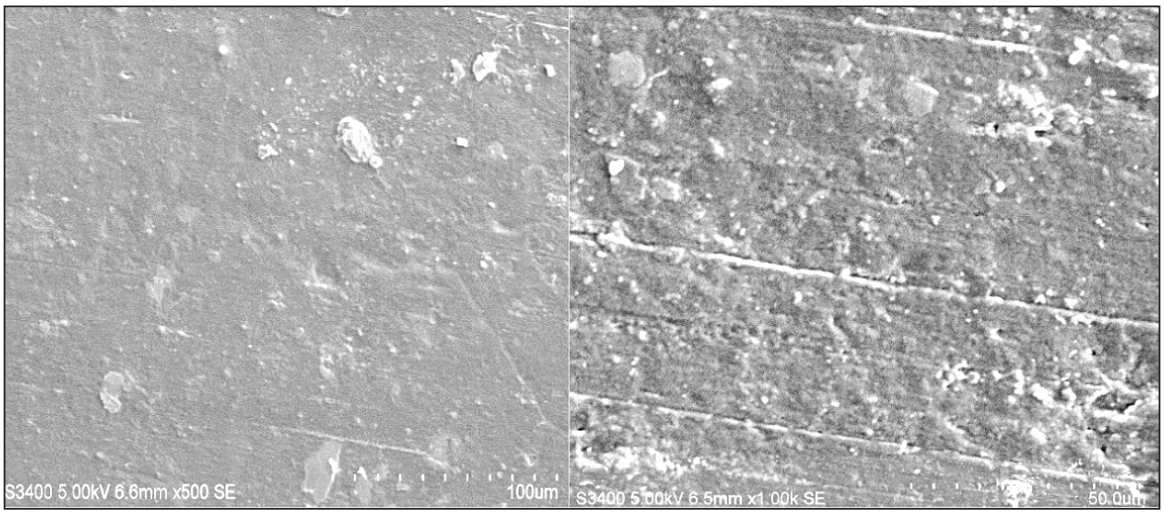

Fig. 5: SEM characterization of optimized formulation

terms. Concentration of glycerin (B) and concentration of SSG have a fluctuating effect on the folding endurance. It can be interpretated in depth through the 3-dimensional plots. The positive coefficients of the main effects and negative coefficients of the quadratic terms suggest that the effect exerted by these factors is complex and, perhaps, concentration dependent.

In vitro dissolution and drug release at 30 minutes

It is clear from the equation (iii) that concentration of Soluplus® has a negative impact on the drug release. Higher is the amount of Soluplus®, lower will be the drug to polymer ratio and slower will be the release. The polymer matrix opposes the release of drug through the matrix into the medium, thereby delaying the rate of drug release. Concentration of glycerin (B) and that of SSG (C) aids the dissolution procedure and facilitate the drug release. It is proved from the release patterns recorded in Fig. 4 that the release profile that the optimized ODF provides release profile superior to the marketed orally dispersible tablet product. ODT provides slightly higher burst release in the initial few minutes, but complete

release is achieved earlier by the film. Thus, the ODF proves to be a better alternative for the immediate release of KT.

Scanning electron microscopy

The surface uniformity is attributed to the mixing efficiency of twin screws of HME. Efficient mixing has resulted in even surface uniformity and uniform distribution of KT the ODF matrix. The uniform vertical ridges are present throughout the film surface. These ridges have been formed during continuous manufacturing of the film to obtain uniform thickness by stretching the film on a conveyer belt.

CONCLUSION

ODF of KT was formulated and analyzed successfully with statistical validation by HME technique. The ODF provided a rapid release profile over the available marketed product without compromising on the patient compliance. Hence, it can be stated with affirmation that HME is a convenient, feasible process for formulation of patient compliant ODF for amelioration of dental pain.

ACKNOWLEDGEMENT

The authors would like to thank All India Council for Technical Education (AICTE) for the National Doctoral Fellowship and Research Contingency. The authors would like to thank Ms. Sukhada Shevade for help in texture analysis.

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