PROCESS OPTIMIZATION OF CONTROLLED RELEASE OSMOTIC PELLETS OF MEBENDAZOLE SOLID DISPERSION

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Abstract

Objective: Mebendazole is a high potential drug for Hydatid Cyst have short elimination half-life (2.5-5.5 hours) and poor aqueous solubility (0.0387 mg/ml) has been a major issue in achieving adequate oral bioavailability followed by high dose of mebendazole causes many adverse effects like anemia and liver damage.

Methods: The solid dispersion osmotic pellets were developed using extrusion-spheronisation method. A 3^2 full factorial design was applied for the process variables [time and speed of spheroniser] optimization. Different coating levels [%w/v of ethyl cellulose-ethanol-water ternary mixture] respectively coated, to obtain the smooth optimized pellets with controlled delivery of mebendazole. The developed pellets were evaluated for flow properties, Aspect ratio, roundness, drug content, solubility, size, surface morphology and *In-vitro* drug release.

Result and discussion: The optimized batch was prepared by keeping the independent variables spheroniser time, X_1 at 44.429 minute, and spheroniser speed, X_2 at 731.165 rpm to achieve aspect ratio of 0.98, and roundness 89.25%. Optimized formulation (M2) of pellets with 18%w/v coating strength of ethyl cellulose-ethanol-water ternary mixture showed only 48.25 % controlled In-vitro release till 12 hr.

Conclusion: In the present work controlled release osmotic pellets system, are developed together in one system to improve the solubility, dose uniformity and reduce the risk of dose dumping to achieve the desired drug release profile.

Key Words: Mebendazole, Solubility enhancement, Solid dispersion, Osmotic Pellets, Ternary mixture, 3^2 full factorial design.

Introduction:

Nowadays, one of the most common problem encountered with the drugs undergoing development is dissolution. Approximately 60% of the newly discovered drugs exhibit solubility related problems[1]. Solubility and dissolution are the key determinants of a drugs oral bioavailability and are also the rate-limiting steps in the drug's absorption from gastrointestinal tract[2]. To overcome this pharmaceutical problem, many solubility enhancing technologies have been developed which includes solid dispersion (SD), nanocrystals, cyclodextrin complexes and lipid formulations. SD is now firmly recognized as a technology for the development of low aqueous solubility drugs, which is reflected in the number of FDA approved products in recent years[3]. Improvement in the oral bioavailability of BCS class II dugs of Biopharmaceutics Classification System (BCS) is one of the most difficult task in formulation development[4]. Larva of the parasite Echinococcus granulosus or E. multilocuralis, causes Human echinococcosis, it migrates to the various body parts via systemic circulation[5]. Literature supports that, at present surgery is the only treatment for patients infected with the larva of Echinococcus granulosus or E. multilocuralis, but it is unsuccessful due to extended secondary alveolar echinococcosis. So it is suggested that a productive drug management with chemotherapy is required prior or post-surgery. Mebendazole (MBZ) is the drug of choice for alveolar echinococcosis, which needs uninterrupted treatment for a minimum period of two years and long- time patient monitoring[6]. However, like other BCS class II drugs, its poor solubility[7] and bioavailability[8], limits its use for the effective treatment of alveolar echinococcosis[9-10]. So it is needed to enhance the drug's gastrointestinal absorption[11] and bioavailability by addressing the solubility of the drug. Multi-particulate systems like microspheres, beads, pellets, etc. offers their distinct benefits over the other conventional dosage forms such as tablets and capsules. These systems also provide more stable plasma concentration and less chances of local side effects[12-13]. Pellets as a Multi-particulate drug delivery system provides therapeutic benefits like reduced irritation of the gastro-intestinal tract and a lesser chances of side effects due to dose dumping[14]. Moreover, pellets can be easily coated which renders them appropriate for sustained drug delivery[15]**.** Osmotic pumps are most encouraging strategy-based devices for controlled drug delivery[16].

Osmogens are the crucial component of the osmotic pumps.When the osmotic pump is exposed to the biological fluids, the fluid penetrates inside the pump through the semipermeable membrane, and dissolves the osmogens present there, which develops a osmotic pressure inside the pump and forces the drug outside through delivery orifice[17]. Controlled porosity osmotic pellet (CPOP) system was developed with osmogen (KCl) and wherein pellets were coated with ethyl cellulose-ethanol and water as ternary mixture. Rate of drug release from CPOP relies on many parameters such as coating thickness, drugs solubility in the tablet core, and extent of leachable pore-forming agent[18-19]**.** Vermox and Emcerm are two marketed preparations used for the treatment of helminth infections and MBZ as drug of choice is available as 100 mg chewable tablets. These are immediate release formulation which requires frequent dosing and can lead to dose related adverse effects like MBZ-associated leukopenia,[20] and granulomatous hepatitis[21]. Since treatment of alveolar echinococcosis, needs uninterrupted treatment for a minimum of two years, there is a need to formulate MBZ controlled release formulation to reduce dose, and dosing frequency and to enhance patient compliance.

MATERIAL AND METHODS

Materials

MBZ was received as a free sample from Balaji Drugs Gujrat, Bharat. Different grades of Polyethylene Glycol (4000.6000, 8000) and microcrystalline cellulose were purchased from S.D. Fine-Chem Ltd, Mumbai. All other ingredients used in the formulation and coating of pellets were of analytical grade.

Process Optimization of Pellets by 3^2 Factorial Design

The critical steps of pellet formulation process were optimized using a 3^2 full factorial design [22]. Table 1 depicts all the variables and their levels. The response surface quadratic model united with the factorial design was applied to determine the impact of spheronisation Speed and time on the angle of repose and roundness. Based on the preliminary batches different levels (-1,0, +1) of process parameter were selected. The spheronisation speed and (X_1) and spheronisation time (X_2) were chosen as the independent variables to optimize the aspect ratio (Y_1) and roundness (Y_2) of the pellets as dependent variables. The polynomial Equation (1) is

$$\boldsymbol{Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_1X_1^2 + b_2X_2^2}$$-----Equation (1)

The terms XY represent the interaction and X_1^2 and X_2^2 represent quadratic terms.

Table 1: 3^2 full factorial design: Target values of dependent variables and levels of independent variables along with their transformed values for process Parameter.

Independent variables	Level		
	Low (-1)	Medium (0)	High (+1)
Spheronisation time (X_1)(minutes)	15	30	45
Spheronisation speed (X_2) (rpm)	300	600	900
Dependent variables			
Aspect Ratio (Y_1) (0.95-1.0)			
Roundness (Y_2)(> 85)			

Formulation of solid dispersion (SD) of MBZ

SDs of MBZ were formulated by melting method using various carriers like PEG 4000, PEG 6000, PEG 8000 and Poloxamer 188. Varying weight ratios of drug: carrier, 1:1, 1:2, 1:3 for optimization of suitable carrier were used. A physical mixture was obtained by dry blending of drug and carrier with help of spatula. The physical mixture was then heated 10^{o}C above the melting point of each carrier for 5 minutes with constant stirring to ensure homogeneity of dispersion. The molten mass was then brought to the room temperature. The cooled mass was then crushed with a mortar and pestle and passed through sieve of 60 mesh size[23].

Formulation of MBZ-loaded solid dispersion core pellets (SDCP)

The MBZ- SDCP were developed by extrusion-spheronisation method (Mini Extruder-Spheronizer, Cronimach Machinery, Gujarat, Bharat). SD containing drug and polymer (1:1), Avicel PH 101(50 gm) and potassium chloride (45gm) as an osmotic agent were added, followed by mixing and sieving through 400 µm sieve. The above mixture was kneaded using water as a binder to prepare a conglomerate of desired plasticity. The kneaded mixture was then extruded through the extruder and the extrudates so obtained were instantly spheronised to form the SDCP. The MBZ -SDCP so obtained were then dried in an oven at 40 ^{o}C for 24 hours[24- 25].

EVALUATION OF SDs:

Solubility Estimation of drug in 0.1N HCl using different carriers:

The saturation solubility of the prepared SD was measured by adding excessive amount of SD in10 ml solvent such as 0.1N HCl. In order to obtain the saturated solution, the SD and solvent mixture was constantly shaken for 24 hours using an orbital shaking incubator. After 24 hours, the solution was passed through cellulose whatman filter paper of 0.45µm pore size. The filtrate was diluted as required, and absorbance was recorded on UV spectrophotometer at λmax 235 nm. The experiment was carried out thrice[26].

Estimation of drug content in SDs

For drug content analysis SD equivalent to 100mg MBZ were dissolved in minimum amount of methanol and then volume was made up to the 100 ml using 0.1N HCl in a volumetric flask. The solution was then passed through a 0.42 µm whatman filter paper and the clear liquid so obtained was analyzed for drug content using UV-Visible double beam spectrophotometer at

235 nm. The experiment was repeated thrice, and the average drug contents were determined in the prepared SD[27].

EVALUATION OF SDCP

Flow properties and Friability test

The flow properties of MBZ loaded SDCP were characterized by the estimation of angle of repose, Hausner's ratio, and Carr's index. Roche Friabilator (Model TA3 R, Eureka, Bremen, Germany) was utilized for the determination of friability. The friability test was carried out by placing 3 grams of uncoated SDCP in the drum, and tumbling it at 25 rpm for 4 min. The percent weight loss of SDCP before and after the experiment was used to calculate % friability[28-29].

Pellet Roundness, Aspect Ratio and Size

SDCP can be comfortably coated and packaged in capsules, but to be effectively processed size and shape are key parameters. For the evaluation of pellet shape aspect ratio and roundness are the crucial parameters[30]. The roundness, aspect ratio, and size of the pellets were studied using the image analyser connected with a computer system enabled with a video camera (Olympus SP-350, Tokyo, Japan) and optical microscope (Olympus CX31, Tokyo, Japan). The digitised images were analysed by the Magnus Pro Version 3.0 Software (JSM 6510LV, MA, USA)[26].

Surface Morphology

The surface morphology, shape and thickness of coating was analysed with the help of scanning electron microscopy.

Drug content of SDCP

MBZ loaded SDCP were weighed and crushed. The crushed pellets equivalent to 100 mg of the MBZ was accurately weighed and dissolved in 20 ml of methanol using sonicator for 20 min. The volume was then made up to 100ml with 0.1N HCl. The Solution was then passed through Whatmann filter paper and the filtrate was diluted as required with 0.1N HCl. The absorbance of the diluted solution was recorded at 235 nm and the % drug content was calculated[26].

Coating of SDCP in fluidised bed Coater

Coating solution was prepared by dissolving 12, 15, and 18% w/v of ethyl cellulose in ethanol, followed by stirring and sonication for an hour. To the coating solution dibutylpthalate, and talc were added as plasticizer and glidant, in 10 and 5% w/w of dry polymer concentration, respectively. 100 g of MBZ loaded SDCP were coated in a bottom type spray fluidised bed coater (Cronimach Machinery, Gujarat, Bharat). After coating of the SDCP with different concentrations of ethyl cellulose coating solution, the SDCP were dried at 40°C for 5 min in an oven. Fluidised bed coater was operated at the following processing conditions: Inlet temperature = 40–45 °C, outlet temperature = 30–35°C, nozzle diameter = 0.7 mm, atomisation pressure = 2.0 bar, and spray rate =10 g/min[31].

***In-vitro* drug release study**

In-vitro drug release was studied in order to determine the impact of coating and pH of the dissolution fluid on the release of MBZ from the coated SDCP. The study was performed on coated SDCP (equivalent to 100 mg of drug) using U.S.P type I dissolution apparatus. 900 ml of 0.1M HCl was used as the media for the study (pH 1.2, 100 rpm, 37 ± 0.5°C)[32]. At fixed time periods the samples were withdrawn and the amount of MBZ released was determined

using UV/Visible spectrophotometer at 235 nm. The release pattern of the MBZ was studied by plotting the graphs of percent drug released versus time. All the experiments were repeated thrice and the values represent given here are mean ± SD.

RESULT AND DISCUSSION

MBZ - Excipients Compatibility Study

Differential Scanning Calorimetry (DSC)

The melting endotherm of MBZ is shown in the Fig 1 at 288.69°C. The endothermic peak of drug was absent in SD. Literature suggests that the SD contains amorphous form of the drug. These results demonstrated the formation of SD of MBZ suggesting the change of state from crystalline to amorphous, which is the reason for improved solubility of Drug[33].

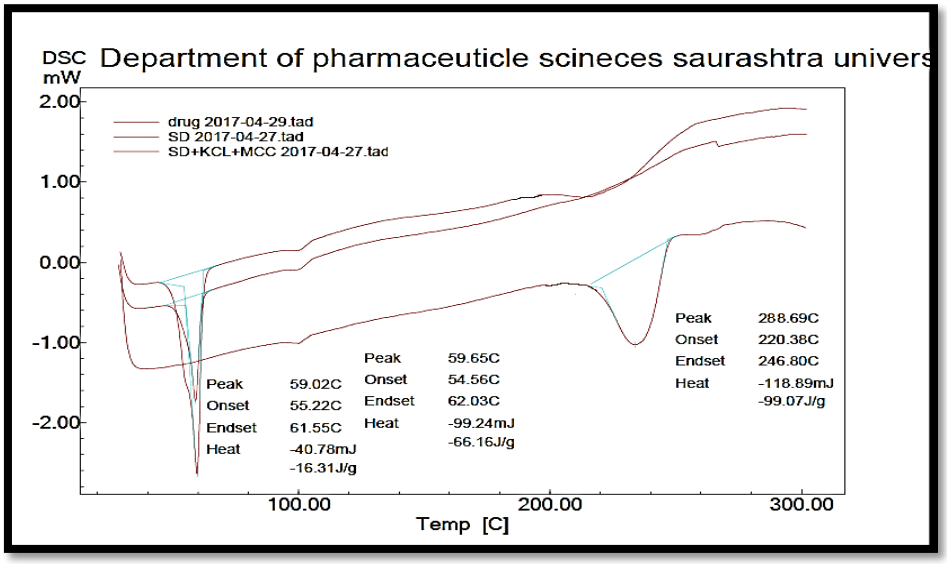

Fig. 1: Overlay DSC spectrum of Mebendazole , SD, and SD+ KCl+ MCC

Characterisation of SD

Solubility study

Table 2 shows the solubility data of drug with different carriers (PEG 4000, PEG 6000, and PEG 8000) in different ratio's (1:1, 1:2, 1:3). The solubility studies were performed in 0.1N HCl. The drug's solubility improved the most when PEG 4000 was used as a carrier. According to a review of the literature, the medication was found to be fully absorbed from PEGs with a reduced molecular weight. Here PEG 4000 was used to generate the SD for the formulation of pellets because of its low molecular weight and surfactant properties[6-34]. It was observed that solubility of drug is maximum with PEG 4000, but no considerable improvement in the solubility of MBZ was noticed with an increase in the drug to carrier ratio. Hence the minimum ratio of Drug: Carrier (1:1) was selected for further studies.

Table 2: Solubility of drug in SD

Reported Solubility of drug = 0.0125mg/ml			
	Solubility(mg/ml) of drug in various carriers		
Drug: Carrier	1:1	1:2	1:3
PEG 4000	0.312±0.0125	0.364±0.018	0.395±0.019
PEG 6000	0.087±0.0129	0.098±0.016	0.108±0.011
PEG 8000	0.125±0.019	0.135±0.02	0.188±0.014

All Value expressed as mean± SD (n=3)

Characterisation of SDCP

Micromeritics properties of core pellets

The Table 3 shows the parameters, friability, drug content and practical yield of core pellets. The Carr's index from 5-15% and the Hauser's ratio from 1.0 -1.17 indicate excellent flow. The flow properties are considerably affected by the size and shape of the pellets[30]. Friability study reveals that SDCP requires adequate mechanical strength further coating process Fluid bed processor. Friability of less than 1% is acceptable according to Indian Pharmacopeia 2010. All the batches F1 to F9 has acceptable friability which complies with the I.P. limits[35]. Drug content was present in the range of 83±0.028 to 89±0.07 indicating the efficient mixing of drug in the blend. Practical yield was found to be in the range of 75±2.4 to 85±4.5 gm. which reflects suitability of method of preparation of pellets.

Table 3: Micromeritic Properties, Drug content and Practical yield of Core Pellets

Batches	Angle of repose	Carr's Compressi-bility index	Hausner's ratio	Friability (%)	Drug content (%)	Practical yield (gm)
F1	33.4±2.35	7.86±0.65	1.08±0.01	0.8±0.001	84.12±0.052	75.56±2.4
F2	23.2±3.21	5.0±0.45	1.05±0.002	0.9±0.001	88.02±0.025	80.06±4.4
F3	28.2±3.38	14.86±0.29	1.17±0.01	0.8±0.002	89.51±0.07	74.16±5.4
F4	32.2±2.89	6.0±0.80	1.06±0.011	0.7±0.001	86.31±0.015	78.46±6.1
F5	25.2±2.65	10.52±0.57	1.11±0.017	0.8±0.002	87.15±0.06	74.24±5.9
F6	26.2±3.1	8.33±0.38	1.09±0.013	0.7±0.001	82.15±0.04	75.26±6.8
F7	33.4±3.71	6.6±0.61	1.06±0.015	0.8±0.001	78.23±0.50	79.35±5.4
F8	22.3±2.78	5.95±0.33	1.06±0.014	0.9±0.003	83.52±0.028	82.26±3.3
F9	32.5±2.89	6.57±0.48	1.07±0.012	0.6±0.002	85.61±0.018	85.34±4.5

All Value expressed as mean± SD (n=3)

Surface morphology studies of core and coated pellets

Surface morphology and coating thickness of SDCP (Fig. 2) was analysed using SEM. SEM images are showing the coating thickness of the polymer ethyl cellulose-ethanol-water ternary mixture. The average coating thickness of 55.0µm indicates that the pellets are coated with uniform thickness of polymer ethyl cellulose. SEM images depicts that the inevitable irregularities such as fissure and pores created during pelletization were virtually disappeared after coating of SDCP.

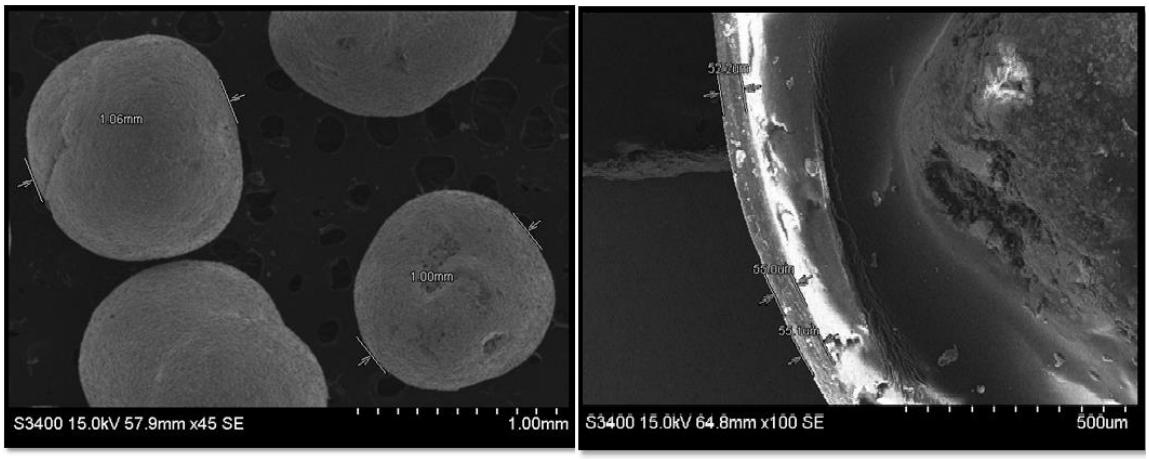

Fig. 2: Scanning electron micrograph (SEM) (a) core pellets (b) optimised coated pellets

Optimization, Data Analysis and Model Validation of drug-loaded uncoated core pellets: Fitting of Data to the Model

Two independent variables, X1 and X2 and their 3 levels in real and coded values are given in Table 1. The dependent variables, Y1 and Y2 were observed to be in the range of 1.01±0.01 to 1.62±0.01 and 75.5±3.6 to 89.1±6.8 % respectively. Different models were applied Design-Expert software on the results obtained for all the 9 formulations. The best fitting model for both of the dependent factors, Y1 (Aspect Ratio) and Y2 (Roundness) was obtained to be quadratic model. The values of R^2, adjusted R^2, predicted R^2 and %CV (coefficient of variance) are shown in table 4. From the details shown in table 4 it is clear that all the models applied were found to be significant at the 5% confidence level since $P \leq 0.05$ for both the responses, aspect ratio and roundness. CV describes the reproducibility of a model, and it is defined as the ratio of the standard error of the estimate to the mean value of the observed response. Models are reproducible for both the responses, aspect ratio and roundness, since % CV is not greater than10% and a model is regarded reproducible only if its % CV is less than 10%.

Table 4 - Summary of results of regression analysis for the responses.

Response(Y)	P value	R^2	Adjusted R^2	Predicted R^2	Adequacy precision	%CV
Y_1 (Aspect Ratio)	0.0075	0.9828	0.9542	0.8695	13.604	3.44
Y_2 (Roundness)	0.0012	0.9951	0.9868	0.9421	30.106	0.70

Optimization and Validation

A desirability outlook was used for numerical optimization technique to produce concise settings for the formulation. The process was optimized for responses such as Aspect ratio (Y1) and Roundness efficiency (Y2). The smallest aspect ratio and greatest roundness, were the criteria for selecting the optimized formulation of core pellet. Experimentally Batch F5 was nearest to the opting criteria. The results were again re-established by the overlay plot shown in Fig. 3(C). The yellow portion of the overlay plot is the area where all the selection criteria are fulfilled. Optimized formulation (M2) comes in this yellow portion (depicted by a flag in Fig. 3C)), it indicates that the formulation having the spheronization time (44.429 minutes) and

spheronization speed (731.165 rpm) possesses the desirable characteristics. To check the reliability of the model applied a new random formulation (M1) was formulated. It was observed that the predicted and actual values were in reasonable agreement which indicates the reliability of the optimization technique. Hence, further *in-vivo* studies were carried out on M2 batch. Furthermore, it can be surmised that the regression equations describe the impact of chosen independent factors.

Data analysis for Aspect Ratio (Y_1)

The data of aspect ratio (Y_1) (Table 5) shows broad variations in the range of 1.00 ± 0.01 to 1.82 ± 0.02, which suggests the impact of chosen independent variables on the dependent variables. The quadratic polynomial equation for aspect ratio, Y_1 is given below:

$Y_1 = 23.12-3.2X_1 -0.63X_2-0.67X_1 X_2 + 6.67X_1^2+0.067X_2^2$ ……Equation 2

From equation 2, it is clear that variables X_1 (spheroniser time, $b_1= –3.2$, $p<0.01$) and X_2 (spheroniser speed, $b_2= –0.63$ and $p<0.01$) had shown considerable effect on aspect ratio. The values of coefficient b_1 and b_2, reflects that the spheroniser time is the major contributing factor as compared to spheroniser speed on the aspect ratio. A negative coefficient for X_1 and X_2 suggests the desirable influence on the aspect ratio. As mentioned by the Hileman *et. al* (1993)[36] and supported by S Pandey *et. al* (2018)[25], initial splitting of extrudes is trigged by the spheroniser's speed and the roundness of pellets depends on the frequency and magnitude of collision between the pellets. Prolonging of spheronisation time produces pellets with the smooth surface, maximum roundness, narrow size distribution, high crushing strength, and low friability[36-37]. These are crucial parameters which determines the flow pattern and coating of the pellets. Hence, we could say that the speed and time of spheronisation are the key factors in the development of pellets, since they can significantly influence the ultimate shape and texture of pellets.

Data analysis for Roundness (Y_2)

The roundness (Y_2) data for all formulations (Table 5) was scattered in a range of 75.5±5.65 (minimum) to 89.1±6.11 (maximum). Equation (3) refers to polynomial equation (full model) for response Y_2. The observed value of roundness for all nine batches varies from 75±0.001 to 89±0.015. The observed response clearly indicates that the Response Y_2 is strongly influenced by the two Independent variables. The batch 5 shows highest Roundness of 89±0.015

$Y_2 = 82.51+ 5.55X_1 + 1.60X_2 -0.68X_1 X_2 + 1.08X_1^2-0.067X_2^2$……Equation 3

Both the variables, X_1 (spheroniser time, $b_1= 5.55$, $p<0.01$) and X_2 (spheroniser speed, $b_2= 1.60$, $p<0.01$) produces a significant ($p<0.05$) positive impact on the pellets roundness, which reflects the considerable influence of spheroniser speed and time. The positive sign of coefficient shows that as the speed and time of spheronisation increases the pellets roundness also increases. The statistics suggests that the spheroniser time is more important factor in influencing the smoothness and roundness of the pellets as compared to the spheroniser speed.

Table 5: Design Matrix and measured values of Aspect ratio and roundness of coated pellet
(Mean ± SD, n=3).

Batches	X1 (Spheronizer time)	X2 (Spheronizer speed)	Aspect Ratio (Y1)	Roundness (Y2)
F1	(15)-1	(300)-1	1.32±0.05	75.5±5.65
F2	(30)0	(300)-1	1.42±0.02	80.4±5.99
F3	(45)1	(300)-1	1.62±0.015	88.8±4.59
F4	(15)-1	(600)0	1.25±0.04	78.6±5.4
F5	(30)0	(600)0	1.01±0.01	89.1±6.11
F6	(45)1	(600)0	1.35±0.01	82.1±7.03
F7	(15)-1	(900)1	1.15±0.08	79.9±6.98
F8	(30)0	(900)1	1.25±0.01	84.7±678
F9	(45)1	(900)1	1.42±0.02	79.7±4.98

All Value expressed as mean± SD (n=3)

Contour Plot

Regression equations are graphically presented in the form of the contour plots, to show the relationship between the response and experimental levels of each factor. The contour plots for variables Y_1 (Aspect ratio) and Y_2 (Roundness) are depicted in Fig. 3 (a and b) respectively. Fig. 3(a) shows a linear relationship with factor X1 but exhibits curvilinear relationship for Y_2.

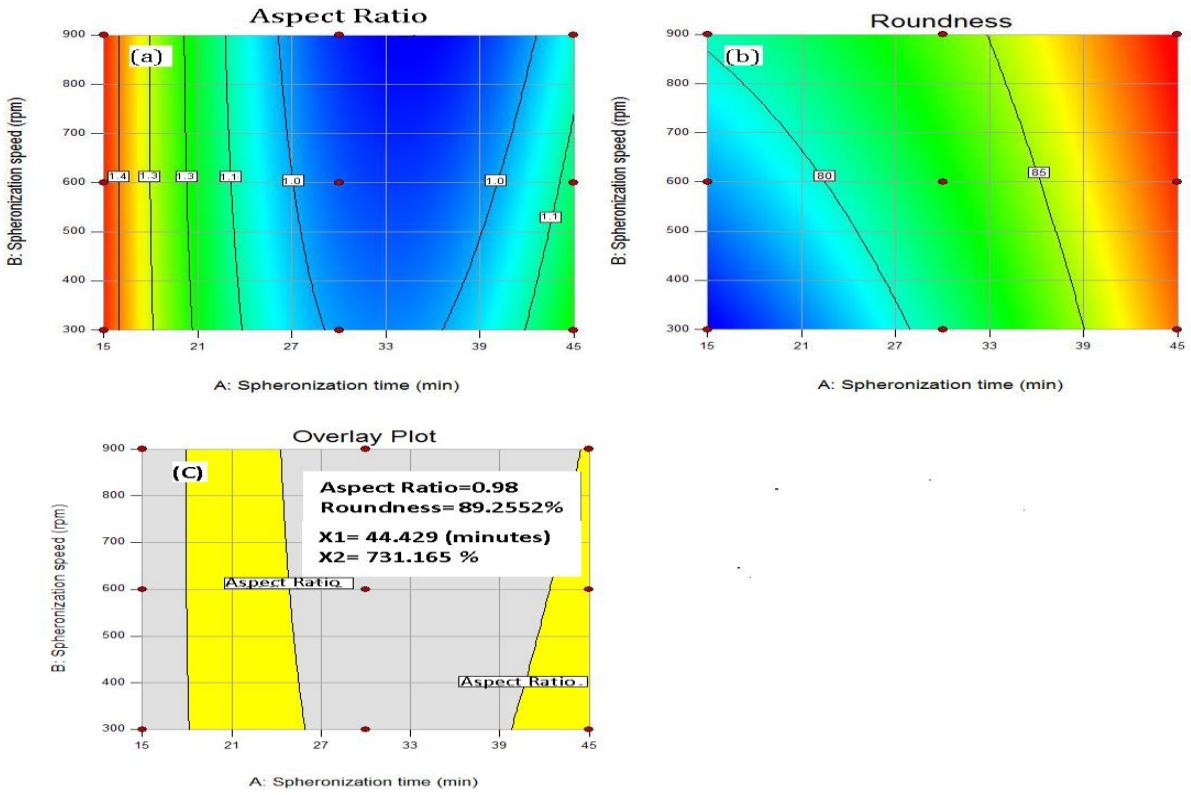

Fig. 3: Contour plots showing influence of Spheronizer speed (X_1) and Spheronizer time (X_2) (a) Aspect Ratio(Y_1), (b) Roundness (Y_2) and (c) Overlay Plot of Optimized Batch.

In-vitro Drug Release Study of Coated Pellets

In-vitro drug release experiment was performed on the Optimized Batch (M2). Different coating concentrations of ethyl cellulose-ethanol-water ternary mixture 12%, 15%, 18% coating level showed release of MBZ for up to 24 hours. The infuence of coating level on the MBZ release rate is depicted in the fig. 4. The plot indicated the delay in the release rates by increasing coating levels. In the present study, SD of drug is incorporated into multiparticulate pellets containing potassium chloride as an osmotic agent, which was coated with ethyl cellulose-ethanol-water ternary mixture. Ethyl cellulose is most widely used polymer because it has good film forming property and provides physicochemical and mechanically stable film. Due to the dense structure of ethyl cellulose it has lower water permeability which makes it difficult to control the drug release rates. Literature report suggests that, the density of ethyl cellulose film could be controlled by changing ethanol water ratio of the solvent[38]. Ethyl cellulose-ethanol-water ternary mixture excludes the use of pore forming agent in coating solution and provides desired drug release rates[39]. In the Ethyl cellulose-ethanol-water ternary mixture the pores were formed spontaneously due to the coacervation and gelation of the polymer. The visual and microscopic study showed that the process of pore creation was driven by the phase separation mechanism, wherein the polymer was acted upon by ethanol and water, respectively, as solvents and non-solvents. One crucial step in figuring out the density of the finished film is gelation[39]. Since organic solvents possesses the risk of toxicity and environmental concerns, present study utilized minimum concentration of ethanol[34].

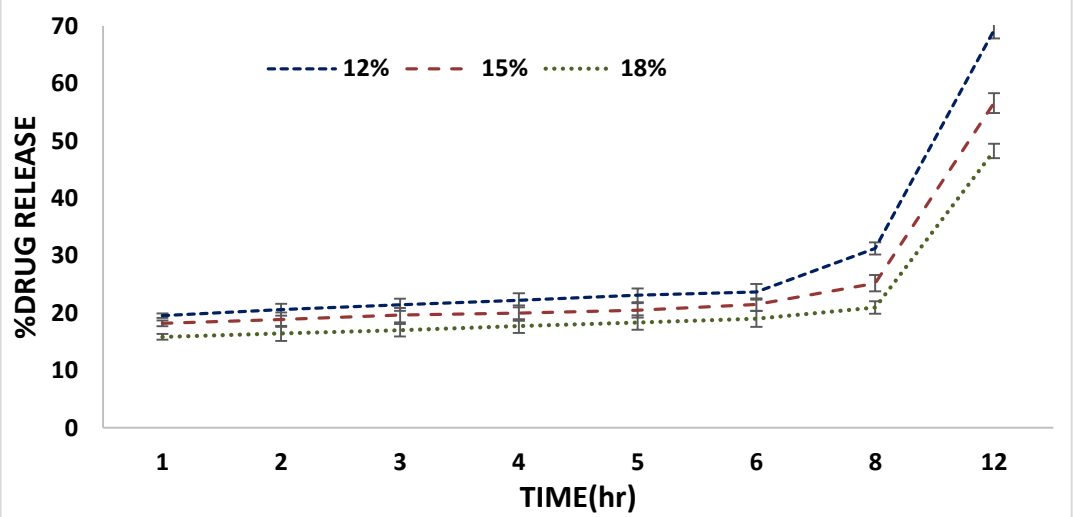

Fig. 4: *In-vitro* drug release profile of coated Pellet

Conclusion

In the present work the controlled release multiparticulate osmotic pellets of MBZ loaded SD was designed. Various carriers were screened for the formulation of SD. SD was developed by the melting technique using PEG 4000 as the carrier. The SD of the drug: carrier ratio of 1:1 was then selected and formulated as Osmotic pellets of microcrystalline cellulose using water as a binder and potassium Chloride as an osmotic agent by using Extrusion Spheronization. Change in the state of drug from crystalline to amorphous in the SD facilitates the solubility improvement.

The two factor three level full factorial design was applied in optimization of, spheronization time (X_1= 44.429 min) and spheronization Speed (X_2 = 731.165 rpm), to achieve, Aspect ratio (Y_1 =0.98) and Roundness (Y_2 = 89.25) of pellets. The optimized pellets were coated with different levels of Ethyl cellulose-ethanol-water ternary mixture to exclude the use of pore forming agent in coating solution and provides desired controlled drug release of drug for up to 24 hours.

Credit authorship contribution statement:

Sonia Pandey: Writing – Original draft review & editing, Validation, Conceptualization. Shweta Pancholi: Work execution and data interpretation, Arti Gupta: Writing – Supervision, Conceptualization. Jitendra singh Yadav: Supervision and data validation, Purnima Tripathi: Writing – review & editing, Conceptualization.

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