ORIGINAL ARTICLE

Utilization of Melt Solidification Technique in the Development of Sustained Release Pastilles of BCS Class –III Anti-diabetic Drug

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Abstract

Aim: Basically, this research work focused to explore the use of solid lipid as alternative to polymers and solvent free process for formulation of sustained release dosage form such as pastilles by making laboratory scale fabricated melt solidification apparatus. **Materials and Methods:** Melt solidification technique was used for the formulation of sustained release pastilles of metformin hydrochloride. For the optimization response surface methodology Box–Behnken design were implemented. **Results:** The lab scale fabricated device was evaluated at 20G size of needle and cooling plate temperature at 4°C.The formulated pastilles was characterized for their size and shape, crushing strength, flow properties, contact angle, % friability, % drug content uniformity, and thermal properties by differential scanning calorimetrty, evaluation of pore formation done by scanning electron microscopic study. The *in vitro* dissolution study revealed sustained release through lipid matrix up to 8–10 h. More than 95% drug released was observed at 10 h. The formulated Pastilles were somewhat spherical in shape and size in the range 2.5–3.5 mm; however, the angle of contact of pastilles was found to be more than 115°. Pore former quantity plays key role, it was enhanced the dissolution rate. **Conclusion:** Pastillation technique is very effective technique for the formulation of pastilles with desired size, shape, crushing strength, contact angle, and with sustained release of drug.

Key words: Melt solidification apparatus, pastilles, pore former, solid lipid, sustained release

INTRODUCTION

The most acceptable route of administration is oral route; it is economical and convenient for administration with more patient compliance and the tablet, capsule and granules, pellets, etc., are most preferable dosage forms.[1] A lipid has wide applications in drug delivery. The formulations of lipid based dosage forms are the best alternative over polymers to develop the different formulation with better the rapeutic benefits. The solid lipids such as fatty acids and triglycerides are utilized as matrix forming agents utilized in the development of modified release dosage forms.[2-4] taste masking of bitter drugs,[5] enhancement of drug solubility and bioavailability[6-8] and formulation of floating drug delivery systems.[9,10] If compare with polymers, triglycerides and fatty acids have many advantages such as cost effectiveness, non-toxicological, and biodegradable.[11]

The multi particulate system of drug delivery mainly consists of many distinct drug enclosing units, in which drug particles are sometimes distributed inside the matrix or enclosed in reservoir, after formulation these multiple units are supplied in capsule and if the dose of drug is large then it is compressed into tablet. This multi particulate dosage form has several advantages such as it reduces risk of systemic toxicity, inter and intra subject variability, dose dumping, variation in absorption also offers better delivery of incompatible drugs together.[12] In the literature, many of polymers are reported that are suitable matrix former that may help to give sufficient release kinetics, such as hydroxyl propyl methyl cellulose, ethyl cellulose and its derivatives,[13] poly (vinyl acetate),[14] and poly (acrylic acid) water-insoluble derivatives.[15] Solid lipids material such as fatty acids and triglycerides have

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Received: 17-09-2022
Revised: 24-10-2022
Accepted: 08-11-2022

abundant ability to hold drug in lipid matrix to retard the release rate to get sustained effect.[16]

There are numerous techniques are used for formulation of lipid-based modified release dosage forms such as melt granulation,[17] hot melt extrusion,[18,19] spray congealing,[20] solid lipid extrusion,[21] extrusion spheronization,[22,23] and supercritical fluid technology.[24] The one more technique that is pastillation process, this technique is used in chemical as well as agrochemical industries for the conversion of liquids into solidification and better for the safe handling of powdered chemicals materials in the form of pastilles, that is, hemispherical solidified discrete units, which is not yet been much more express for its prospective in pharmaceuticals for drug delivery systems. Pastilles are made from melt mass of solid lipids and these are the solidified discrete units. It has benefits that it overcomes the cost of equipment and energy and also ultimately eliminates the dust related with grinding as well ascrushing or other cutting and breaking processes. One more advantage is that this process does not need solvent.[25,26] also the in chemical industry well equipped pastillaton technology already available for large production level processing. The objective this experimental work was to fabricate melt solidification apparatus for the formulation of solid lipid based pastilles, also to optimization of the processing of device for some parameters such as height difference from needle tip to cooling plate, percent drug release, contact angle of pastilles and size of pastilles and as well as to analyze the impact of the pore former as a release rate modifier for the formulation of metformin hydrochloride (MET HCl) sustained release product.

MATERIALS AND METHODS

MET HCl sample generously provided by wokhar dt, Aurangabad, India. Excipients glyceryl monostearate as well as potassium chloride were purchased from DSA Nashik, India. Hydrochloric acid, disodium hydrogen phosphate, sodium hydroxide was purchased as analytical grade. Gelatin capsule shell procured from DSA, Nashik, India.

Method

Fabrication of melt solidification apparatus

Assembling and set up of pastilles formulation apparatus

Laboratory scale in-house assemble device was fabricated [Figure 1] using glass syringe with plunger, hypodermic metal needle (20 G), heating jacket, automatic temperature controller, stand with holder, and ice plate.

Working mechanism

Melted mass of wax/lipid, drug along with excipients was poured in the glass syringe. Heating coil placed in the jacket assembly surrounded with glass syringe was then connected to electricity through automatic temperature auto cut regulator type transformer. Depending on the melting points of substance for low melting substances water jacket heating assembly is utilized. For high melting points substances (thermally stable substances), liquid paraffin (high boiling point) is used in the jacket instead of water. To keep solid lipid material in molten state for the maximum time of duration can be possible by liquid jacket because it uniformly distributes the heat. Just below the tip of syringe assembly, there is cooling plate on to that drops of molten mass falls and that drops immediately get solidify due to cooling temperature of plate controlled by resting the plate on ice cube. It is possible to control the size of pastilles by manually pressing the molten mass with plunger. The screening study was carried out by formulating placebo pastilles by considering key factors such as size of needle, that is, 20 G, 14 G, drop height from needle tip to cooling plate (0.5–2.5 cm), and cooling plate surface temperature (4°C, 10°C, and 25°C).

Formulation of pastilles by use of glyceryl monostearate as solid lipid

Step I

The oil bath with liquid paraffin was used to melt glyceryl monostearate a solid lipid at 65°C.

Step II

MET HCl drug was melted separately at 210–220°C on oil bath assembly.

Step III

Finely powdered potassium chloride (KCl) pore former was suspended along with drug to the melted mass of lipid and was stirred constantly to get homogenous mixture.

Step VI

After that this homogenous mixture was transferred carefully to the assembly of glass syringe which was preheated by constant temperature water heater jacket, as the syringe was preheated the liquefied melt mass was dropped from the hypodermic needle onto the cooling base plate to due to low temperature drop of melted mass get cooled rapidly and gives hemispherical shape pastilles. These hemispherical shape pastilles were then with care scraped out from the cooling plate with help of sharp knife. These formulated pastilles then were transfer in size number "0" capsule shell.

Experimental design by Box–Behnken design

Formulation batches were calculated using 3^3 factorial designs for this Box–Behnken design with 3 -factors, 3-level used and the Design of Expert software (ver. 13.0.5.0, Stat Ease) Minneapolis, USA. Utilized by considering 3 center points gives 15 runs [Table 1]. The influence of operating

variables on the formulation of pastilles was evaluated and optimized by response surface methodology (RSM).

Following operating variables were considered,
(X1): Glycerol monostearate (GMS) solid-lipid,
(X2): KCl pore former
(X2): Dropping height from the cooling plate,

Above three factors was an in-dependable variables which are evaluated at three levels [Table 2].

Whereas the percent cdr (Y*) was dependable variable.

Pastilles characterization

Formulated pastilles of F1-F15 batches were evaluated for morphological characteristics such as color, diameter size, spherical shape, and surface texture [Table 3].

Determination of contact angles

Evaluation of flow property of pastilles depends on contact angle. The photographic method was used to determine contact angle of the formulated pastilles against metallic plate. For this photograph of pastille was taken from one side and was proportionally magnified by processing image in Photoshop software. The contact angle of formulated pastilles was calculated manually using below equation.

$$\theta = 2\,tan^{-1}\frac{2h}{d}$$

Table 1: Formulation batches based on 3-factors, 3 -levels (Box–Behnken design): Factors and their respective responses

Batch code	Factors			Y % CDR response
	X1	X2	X3	
F1	0	–1	–1	96.68
F2	1	0	1	85.14
F3	0	0	0	97.44
F4	–1	–1	0	96.35
F5	0	1	1	95.78
F6	0	0	0	97.41
F7	0	–1	1	90.25
F8	1	1	0	88.16
F9	1	0	–1	89.58
F10	–1	1	0	96.93
F11	–1	0	–1	98.89
F12	–1	0	1	95.45
F13	1	–1	0	84.54
F14	0	1	–1	96.95
F15	0	0	0	97.38

The coded terms,
h: For height of solidified drop form its base.
d: For diameter of solidified drop

Both this dimensions measured from photographic image of pastilles and the contact angle was calculated.

Drug content uniformity

Determination of drug content was done by taking pastilles corresponding to 500 mg of MET HCl was triturate and put in 20 ml distilled water in 100 ml of volumetric flask After that sonicated for 10 min and then keep it to cool at normal condition at 25°C room temperature, with distilled water the rest volume was made up to the mark. 10 ml of the above solution were then filtered using 0.45 um filter then it was dilute accurately with distilled water then analyzed at 233.5 nm on UV spectrophotometrically and drug concentration was calculated by equation.

Standard drug solution was prepared in same manner as described above to calculate percent drug content.

$$X = Y \pm \frac{C}{M} \quad (1)$$

Further, % drug content was determined from the concentration, with below eq.:

$$\%\,\text{drug content} = \frac{\text{concentration of drug in sample solution}}{\text{Equivalent concentration of standard drug}} \times 100 \quad (2)$$

Flow properties

The formulated pastilles were studied for flow properties such as test done bulk density test, tapped density test.

Determination of % friability test

The friability test carried out by weighing sample of 2000 mg pastilles and noted it. This sample was placed into transparent rotating cylinder of friability test apparatus. The instrument was set with 25 rpm for 4 min duration after completion of test pastilles was removed and reweighed. Friability weight losses were calculated by putting weights into the below formula.

$$\%F = \frac{Wo - Wf}{Wo} \times 100$$

Where, Wo: Weight of sample before test
Wf: Weight of sample after test

Test criteria as per IP is test passes when the friability weight losses are not more than 0.1%.

Table 2: Factors and levels in Box–Behnken design

Factors	Levels used		
	-1 (low)	0 (mid)	1 (high)
X1=Solid- lipid GMS (mg)	1000	1500	2000
X2=Pore former KCl (mg)	50	100	150
X3=Dropping Height (cm)	0.5	1	1.5

Table 3: Observations of physical test

Formulation batches	F1 to F15
Color	White
Shape	Hemispherical
Size (diameter)	2.5±0.2 mm to 3.5±0.3 mm
Texture	Smooth surface

Table 4: Flow properties

Flow characteristic	Angle of contact
Poor	60–85°
Fair	85–105°
Good	105–125°

Determination of crushing-breaking strength

The crushing-breaking strength ability was evaluated to check the pattern of fracture made by punch with respect to force applied on pastille. Texture analyzer instrument was used to do crushing strength test. The strength pastilles of optimized batch F5 evaluated by determining crushing strength before and after exposure to dissolution test were calculated by processing on instrument of mechanical texture analysis model CT3, Brookfield, Germany).

Scanning electron microscopic study (SEM)

The surface texture analysis of prepared pastilles of optimized batch F5 was done by high resolution and low resolution scanning electron microscopic instrument (JSM-6390LV, Japan).

Fourier transforms infrared spectroscopy (FTIR) Spectroscopy

FTIR gives information related to the identification and confirmation of unknown materials or known material with reference data, determination of quality or reliability of a sample under test and determination of the number of constituents in a mixture. The samples were processed by ATR method, direct measurement of sample FTIR spectra possible with method. In this method the sample under test place over the high refractive index prism and pressed it properly with knob after passing IR beam of light that is completely internally reflected in the prism and scanned between the wave number 400–4000 cm^{-1} it produces infrared spectra of sample under test. The instrument used for measurement of FTIR was FTIR spectrophotometer (FT/IR 4600 Jasco). The obtained FTIR spectra were compared with the references for an obtained peak of functional groups.

DSE (differential scanning calorimetric study)

It was carried out for optimized batch F5, using instrument star system differential scanning calorimetrty (DSC 1), mettler toledo, Switzerland which is connected to the sub-ambient assembly of liquid nitrogen. Operating conditions of instrument were it runs under nitrogen purge gas with rate of 100 ml/min. Open aluminum pan was used and sample of 2–10 mg was weighed in it and run at speed of 10°C/min from temperature 30–300°C.

Drug release study

The dissolution test apparatus USP II (make Electrolab TDT 8 L) was used to study the drug release profile of prepared pastilles of each batch. For initial 2 h., the pH 1.2 acidic buffer used as dissolution medium of volume 900 ml and the operating conditions was 50 revolution per minute and basket internal temp., maintained at 37.5 ± 0.5°C later 2 h., the buffer solution was changed with volume of 900 ml phosphate buffer pH 6.8 with same operating conditions and continued run for further 10 h. At every time of interval during dissolution study, the 10 ml of aliquots sample were taken out with pipette and sink condition was maintained with same dissolution medium. Sample was then processed by UV spectrophotometric analysis at 233.5 nm and absorbance was recorded.

Determination of release kinetics and release mechanism

After dissolution calculations further it was processed to study the release kinetics and release mechanism, it gives the information about model fitting.

Stability study

Pastilles of F5-batch were kept in 25 ml of high density polyethylene packing bottle, sealed properly and were stored at about 40°C retained at 75% relative humidity in to the stability chamber for a specific duration of 3 months as per international conference on harmonization guidelines. Sample was taken out at specific duration of one; 2 and 3 months were analyzed for the % drug release.

RESULTS

MET HCl embedded hemispherical solidified pastilles were prepared using laboratory level fabricated melt solidification apparatus. The melt solidification apparatus was evaluated to know the influence of different operative variables. These evaluated constraints were then used to formulate placebo pastilles to make next batches. It was observed that the dimensions of pastilles rise from 2.5 ± 0.1 mm to 3.5 ± 0.1 mm with rise in needle orifice from 14G to 20 G. type of cooling plate and its temperature was directly related with contact angle of pastilles. The conversion of molten lipid to solidified state takes maximum time on glass and plastic surface because these both materials are poor conductor of heat, but study revealed that, there was rapid solidification takes place on metallic surface at 4°C controlled cooling temperature. Study also revealed that, with rise in dropping height which considerably decreases the contact angle, which may affected on drug release from pastilles. Hence, this factor was independent variables in factorial design study. Thus from experimental and statistical study it was concluded that fabricated device was optimized at 20 G needle size, cooling plate with metal surface, cooling temperature for best solidification was 4°C ± 0.1°C.

Evaluation of formulated pastilles

Determination of contact angle

The spreading pattern of melt drop after fall on to the cooled surface with respect to solidification was evaluated by determining its contact angle. According to literature study of contact angle of pastilles, it was noticed that contact angle above 90° is more accurate for hemispherical shape pastilles and it is necessary for good flow property at the time of large scale production. It was found that contact angle of pastilles of formulation batch F1-F15 was in the range of 105°–115° [Table 4]. From this it was concluded that, viscosity of molten lipid produces somewhat rigid pastilles on cooling plate to increase the contact angle.

Determination of flow properties, % friability, and % drug content

The flow property of pastilles was determined by calculating bulk and tapped density test, it was calculated using formula,

$$Bulk\ density\left(\frac{gm}{ml}\right)=\frac{weight\ of\ pastilles}{initial\ bulk\ volume}$$

$$Tapped\ dinsity\left(\frac{gm}{ml}\right)=\frac{weight\ of\ pastilles}{tapped\ volume}$$

The friability study done to determine friability weight losses, it was determined using formula, % friability = Avg. of Initial weight in gram – Final weight in gram after re-dusting/Avg. of initial weight × 100.

The observations were recorded [Table 5].

Determination of crushing-braking strength

The crushing-breaking strengths values help to predict breakup capability of the sample of pastilles under test. Figure 2a demonstrates that pastilles before processed to dissolution test needs more force, that is, 32.10N to crush than that of [Figure 2b], crushing of pastilles after exposure to dissolution medium, that is, 28.20 N. It is concluded that, it was happened due to formation of pinholes by the pore former to allow access to liquid dissolution medium in the pastilles make it smoother and softer.

FTIR analysis study

The ATR method was used for FTIR analysis, the pure drug MET HCl and glyceryl monostearate were directly place separately over the high refractive index prism and run scanned between ranges 400–4000 cm^{-1} on FTIR spectrophotometer instrument (FT/IR 4600, Jasco). Similarly the pastilles of optimized batch F5 placed over high refractive index prism and measure spectra. The obtained FTIR spectra of drug, solid lipid, and optimized batch were compared with the respective reference spectra for an obtained peak of functional groups [Figure 3].

It was observed that in IR spectra of MET HCl, the peak showed 3363.25 cm^{-1} -NH stretching of amine, 1624.73 cm^{-1} -NH deformation, 1175.4 cm^{-1}-CN Stretching, 1045.23 cm^{-1}-CH bending, and 937.235-CNC deformation. In IR spectra of Glyceyl monostearate, the peak showed 3308.29 cm^{-1} O-H stretching of alcohol, 2913.91, 2849.31cm^{-1} for Alkanes, 1731.76cm^{-1} C=O stretching of esters of higher saturated acids, 1175.4 cm^{-1} C-O stretching of esters of higher saturated acids, and 1045.23cm^{-1} C-O stretching of alcohol.

The peaks showed no significant changes in material characteristic when MET HCl used with GMS in optimized batch.

DSC analysis study

It works on thermal analysis, that gives information regarding how the materials heat capacity (Cp) changed by temperature. The amorphous and crystalline form of the pure drug and the pastilles understand by the recording temperature changes as

Table 5: Results of bulk density, tapped density, drug content, and friability

Test	Batches F1 to F15	Remark
Bulk density	0.562–0.813 g/ml	Good flow
Tapped density	0.679–0.876 g/ml	Excellent flow
Drug content	95.6–99.8%	Uniform drug content
Friability	0.1%	Passed

well as energy state at the phase transition temp., [Figure 4] illustrates DSC curve of MET HCl, glyceryl monosterate, and also of optimized formulation batch F5. The melting of MET HCl confirmed by endothermic peak at 221–222°C, and at 59–60°C for glyceryl monosterate.

From above observations it was concluded that the, respective peaks of melting was re-appeared at approximately same numerical melting temperature values in the optimized batch.

Scanning electron microscopic analysis

The drug release behavior from pastilles without causing its erosion is very important hence the study of surface of formulated pastilles of optimized batch F5 is very important by SEM analysis.

In Figure 5a, which was at lower magnification optimized batch pastilles seemed as spherical in shaped and surface texture was uniform.

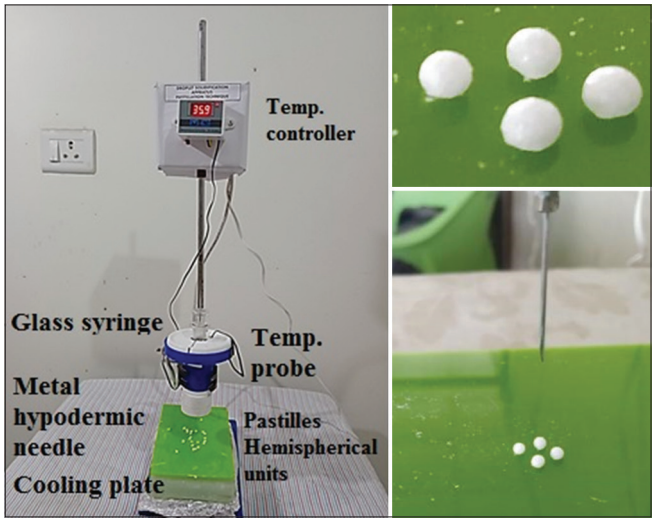

Figure 1: Lab scale melt solidification apparatus

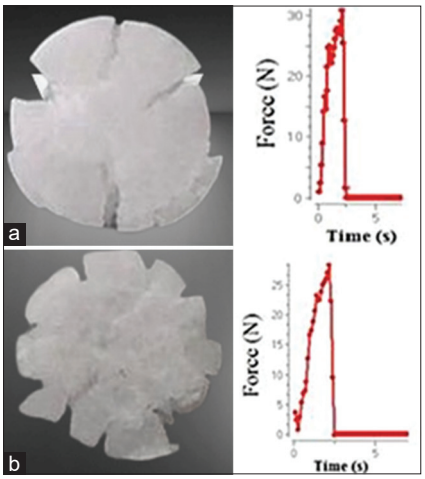

Figure 2: (a and b) Images and plots of crushing strength of optimized batch

Figure 5b shows image taken at higher magnification of pastilles of optimized batch with more crystalline structural flakes were seen on the surface of pastilles.

Figure 5c shows pores on the surface of pastilles, SEM image of pastilles that was taken after exposure to dissolution medium. Thus indicate that there is distribution of solid-lipid to enter in the aqueous medium into the pastilles inside that was observed at higher magnification in [Figure 5d]. It indicates the release of entrapped drug from the pastilles take place due to pore formation by pore former.

In vitro dissolution study

The *in vitro* dissolution study of formulated pastilles of batches F1 to F15 was carried out to k know the effect of glyceryl monostearate a solid lipid matrix forming agent as well as effect of pore forming agent (KCL) and the height difference of needle tip to cooling plate on the release of drug from the pastilles for sustained release in dissolution mediums.

The batch F0, that is, without pore former shows the partial drug release <80% at 10 h of sample [Figure 6b]. This was only the surface adsorbed drug releases, but the remaining drug not releases due to the barrier of lipid does not allow dissolution medium to reach to the entrapped drug which is present inside the pastilles. To get complete release of entire dose of drug from the pastilles the pore former approach was utilized by addition of KCl. This was observed that with increased in quantity of pore former there will be increase in dissolution rate.

Influence of pore former on % release of drug

The influence of the pore forming agent on the release of drug can be done by keeping the quantity of lipid and height from needle tip to the cooling plate was kept constant (F7 and F5, F4 and F10) [Table 6].

It was observed that, while dissolution study; initially the adsorbed drug, that is, adsorbed drug at the surface of pastilles was released and it creates pinholes inside the pastilles and hence the dissolution medium get enter inside the pastilles where the drug present in matrix [Figure 6a and b]. It was concluded that more the amount of pore former incase of (F5), maximum the number of pinholes created into pastilles. Hence, maximum the amount of dissolution medium to the inside core of the pastilles. Study revealed that the release mechanism by which drug was released from pastilles was diffusion, it was considered as the rate controlling factor in the dissolution. This helps to explain the correlation between the quantity of lipid and size of the pastilles formed.

Effect of lipid quantity on drug release

It was concluded that, if minimum concentration of the lipid then lowest the extent of drug get entrapped in lipid

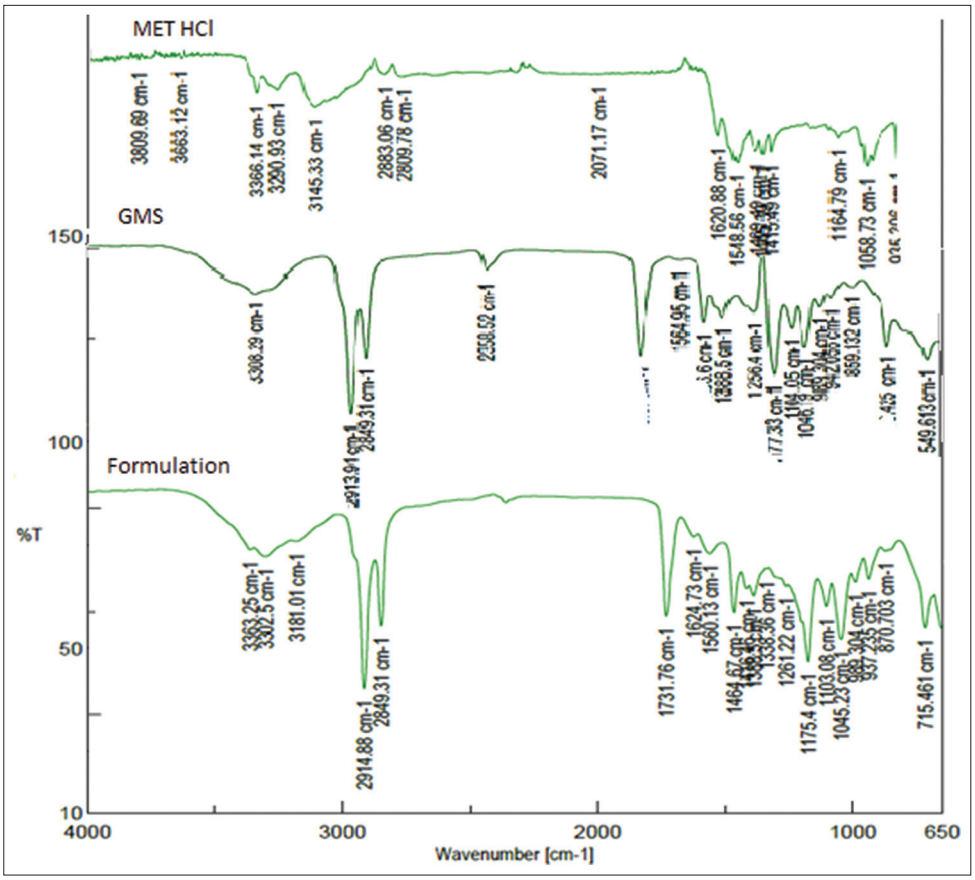

Figure 3: FTIR graph of drug, lipid, and optimized formulation

Table 6: Comparative formulation F7 and F5, F4 and F10 batches

Batch code	Factor		
	X1 (Solid lipid)	X2 (Pore former)	X3 (Height)
F7	0	–1	1
F5	0	1	1
F4	–1	–1	0
F10	–1	1	0

Table 7: Comparative formulation batches F2 and F12, F9 and F10

Batch code	Factor		
	X1 (Solid lipid)	X2 (Pore former)	X3 (Height)
F2	1	0	1
F12	–1	0	1
F9	1	0	–1
F10	–1	0	–1

matrix [Table 7]. But if rise in lipid concentration resulted that may results in inadequate release of drug. Hence, the concentration of solid-lipid has a significant effect in release of drug as shown in [Figure 6c] (F2 and F12; F9 and F11).

Table 8: Comparative formulation batches F7 and F1, F14 and F5

Batch code	Factor		
	X1 (Solid lipid)	X2 (Pore former)	X3 (Height)
F7	0	-1	1
F1	0	-1	–1
F14	0	1	–1
F5	0	1	1
F12	–1	0	1
F11	–1	0	–1

Effect of dropping height on drug release

It was observed that there was direct impact of dropping height on the size of pastilles formed [Table 8]. When the drop of melted mass come out from the needle when it was fall to the cooling base plate if the distance is high then the drop get flatten and it gives less contact angle and release and if the distance is less then it produces hemispherical shape pastilles with improved contact angle and release which also improve the flow property. Effect of these factors clearly observed in [Figure 6a, c, d] (F7 and F1; F14 and F5; F12 and F11).

These operating parameters have impact on release of drug it was also evaluated by response surface plots.

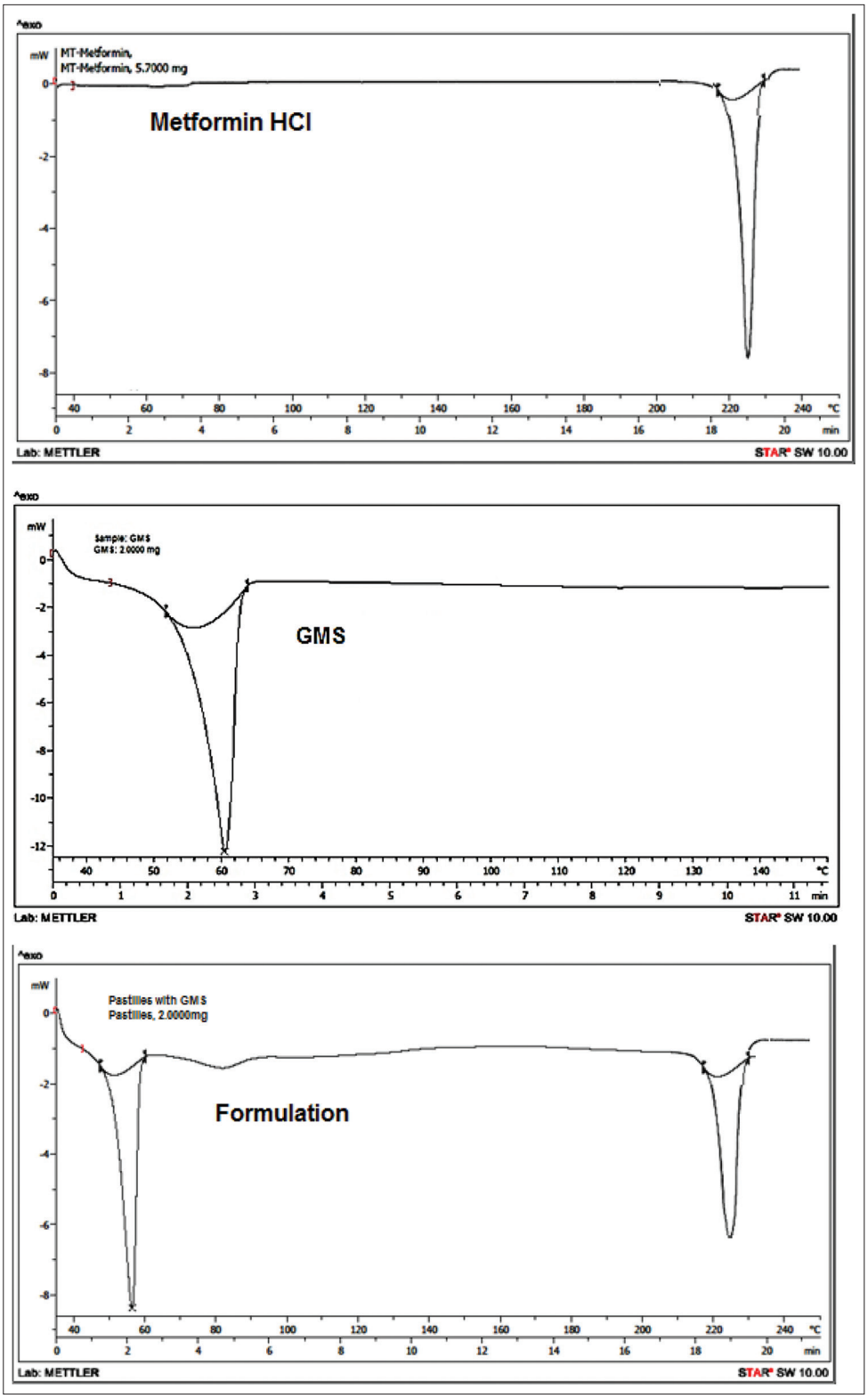

Figure 4: Differential scanning calorimetrty (DSC) profiles of metformin hydrochloride, DSC profiles of glyceryl monostearate DSC profiles of optimized formulation batch

Release kinetics and mechanism

It was concluded that first order drug release model followed by optimized batch F5 and the n value that is the numerical value of Korsmeyer–Peppas found to be 0.6304 along with 0.978 correlation coefficient, it indicates non-Fickian model (anomalous transport). It happened may be due to diffusion and relaxation behavior of glyceryl monostearate in dissolution medium.

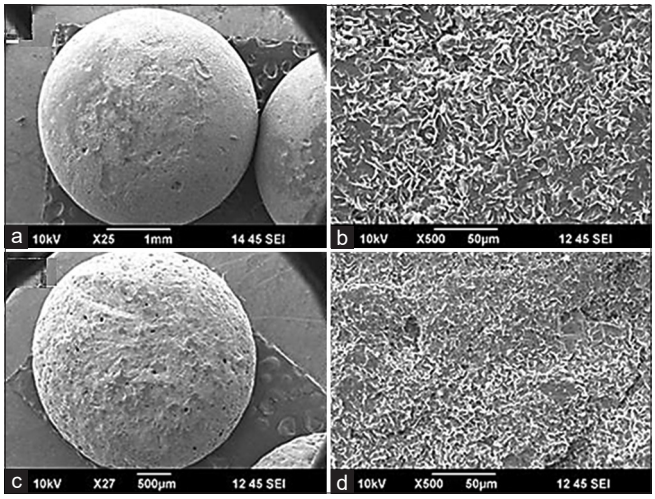

Figure 5: Scanning electron microscopy images of optimized formulation f5 (a) before to placing into the dissolution medium at default magnification, (b) image before placing into dissolution medium at magnification, (c) image after placing in to dissolution medium at default magnification and (d) image after placing into dissolution medium at higher magnification

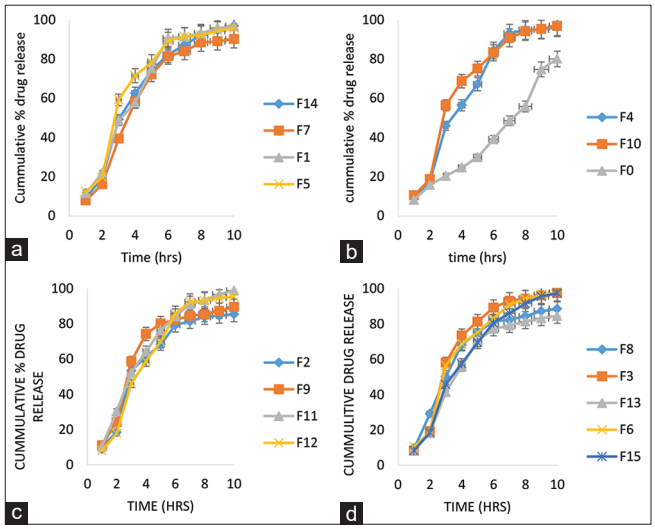

Figure 6: Dissolution profile of (a) f 14, f 7, f1, and f5 batches, (b) f 4, f 10, and f 0 batches, (c) f 2, f 9, f 11, and f 12 batches, (d) f 8, f 3, f 13, f 6, and f 15 batches

Response surface analysis by Box–Behnken design

The statistical correlation between factors as well as variables was characterized by RSM. The combine result of factors such asX_1, X_2, and X_3 was further interpreted by response surface plots. The data fitted with quadratic model and significant with F value 408.69. Furthermore, ANOVA (analysis of variance) was calculated by the software [Table 9]. The correlation among variables and response of percentage cumulative release of drug are shown in equation (8).

$$\%CDR = +97.41 - 5.03A + 1.25B - 1.94C + 0.7600AB$$
$$-0.2500AC + 1.32BC - 4.28A^2 - 1.63B^2 - 0.8625C^2 \quad (8)$$

Coded values,
A for glyceryl monostearate amount, B for KCl amount, and C for height of needle from cooling plate.

Finally, the quantities which were optimized were obtained from design of experiments, glycerol monostearate (1351.185 mg), potassium chloride (146.750 mg), and height (0.807 cm).

Effect of GMS

The relationship in between three independent variables is represented in [Figure 7] 3D graph of response surface. The study revealed that, increase in the release of drug observed with reduction in amount of glyceryl monostearate and increased in concentration of pore forming agent. With the minimum concentration of GMS then there was a lesser amount of drug entrapment in the lipid matrix. The optimized range of GMS to sustained drug release was found to be 1000 (mg) to 1500 (mg) as suggested in [Figure 7]. In correlation between height and KCl, it was observed that there was a positive impact on release of drug from pastilles.

Effect of KCl

The influence of pore former on the % release of drug was assessed by keeping constant the amount of lipid and needle

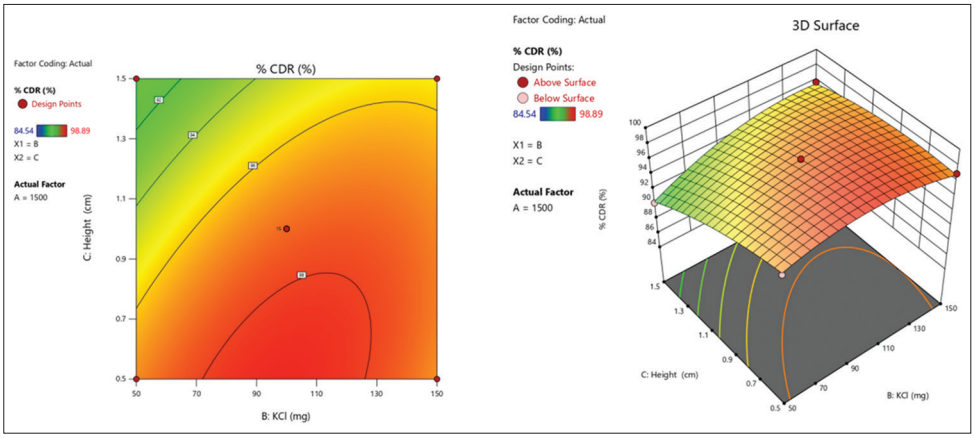

Figure 7: Effect of glyceryl monostearate on drug release with correlation to height

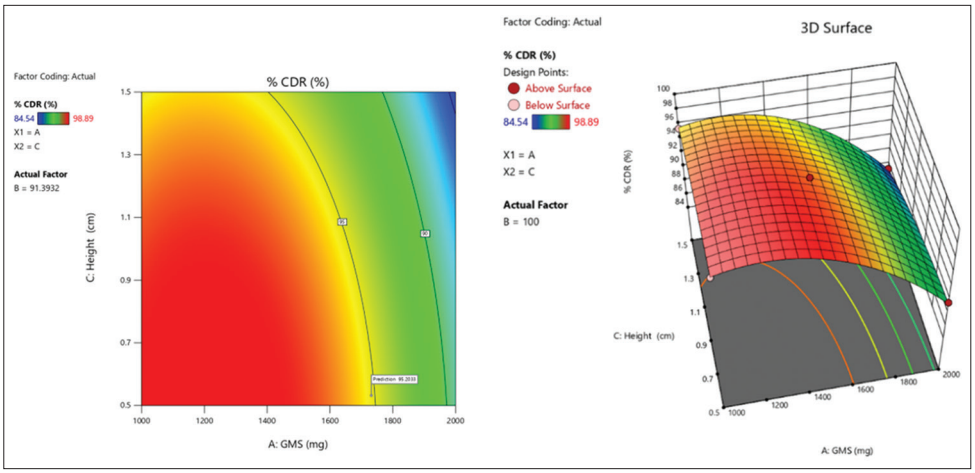

Figure 8: Effect of potassium chloride with respect to concentration of glyceryl monostearate on drug release

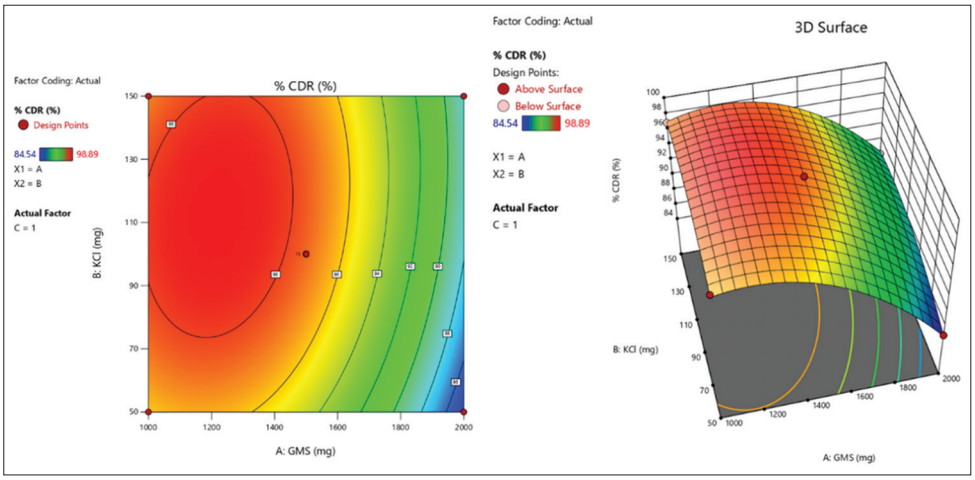

Figure 9: Effect of height with respect to size and shape of pastilles

Table 9: Collective outcomes of analysis of variance with respect to response parameters Quadratic model with ANOVA

Response 1: % CDR (cumulative drug release)

Source	Sum of Squares	df	Mean Square	F-value	*P*-value	
Model	328.68	9	36.52	408.69	<0.0001	(S)
A-GMS	202.01	1	202.01	2260.58	<0.0001	
B-KCl	12.50	1	12.50	139.88	<0.0001	
C-Height	29.95	1	29.95	335.20	<0.0001	
AB	2.31	1	2.31	25.85	0.0038	
AC	0.2500	1	0.2500	2.80	0.1553	
BC	6.92	1	6.92	77.40	0.0003	
A^2	67.72	1	67.72	757.79	<0.0001	
B^2	9.84	1	9.84	110.12	0.0001	
C^2	2.75	1	2.75	30.74	0.0026	
Residual	0.4468	5	0.0894			
Lack of Fit	0.4450	3	0.1483	164.81	0.0060	(S)
Pure Error	0.0018	2	0.0009			
Cor Total	329.13	14				

*(S): Significant

height [Figure 8]. The dissolution medium was entering in to the pastilles. Maximum the quantity of pore former more the pinholes created inside the pastilles, this resulting in increased entry to dissolution media to the inside core of the pastilles. To maximize the extent amount of pore former, it leads to enhancement in the dissolution rate by creating pores on the surface of pastilles.

Effect of height

The size and shape of formulated pastilles were correlated to the droplet falling height from needle to the cooling plate [Figure 9]. The hemispherical shape of the pastilles has more contact angle giving optimum drug release. Along with this it has an inverse relation between the contact angle of pastilles and drug release rate, by maintaining the quantity of lipid and pore former constant, and the amount of solid-lipid and pore former was held at constant.

Stability studies

Stability study was conducted to evaluate the stability of formulation. It was observed that the formulation optimized batch F5 has regularly observed 3 months duration at accelerated conditions of temperature and humidity. It was noticed that there was no any significant change observed in the physical properties as well as in percent drug content also in *in vitro* dissolution study of pastilles [Figure 10].

DISCUSSION

The goal of current work was to formulate sustained release pastilles i.e. a hemispherical shape discrete units) of type – II anti-diabetic drug of BCS Class III the MET HCl by use of lipid excipients as a potential and valuable alternative for polymers to sustained the release of drug by formulating pastilles by novel melt solidification technique. The melt solidification apparatus was successfully developed at laboratory; it was also optimized and successfully used for preparation of pastilles. The identity of MET HCl was confirmed by the physical characteristics, spectrophotometric analysis, and FTIR spectra along with this thermal behavior by DSC analysis. Furthermore, the selection of lipid based excipients such as glyceryl monostearate and stearic acid was done by doing literature survey. FTIR study was conducted to check compatibility between drug and lipid excipients and no interaction was found. For the formulation and development of pastilles, the a blend of drug and lipid were first melt at specific temperature and then poured into preheated syringe of droplet solidification apparatus and a drop of molten mass dropped on to the cooling plate and the pastilles (a hemispherical shape units) obtained. These pastilles were evaluated for contact angle, drug content and SEM, DSC analysis. Separate formulation batches was prepared by using glyceryl monosterate and stearic acid with different pore former such as KCl, Polaxomer 407 and polyethylene glycol (PEG) 4000, PEG 6000. The amount of lipid and pore former has important role in drug release from pastilles. It was observed that, F5 batch of drug with glyceryl monostearate showed drug release up to 10 h. Optimized formulation obtained from by Box–Behnken design of respective lipid excipients for the sustained release drug delivery was prepared and evaluated then compared with F5 batch. It was concluded that there were no significant difference detected.

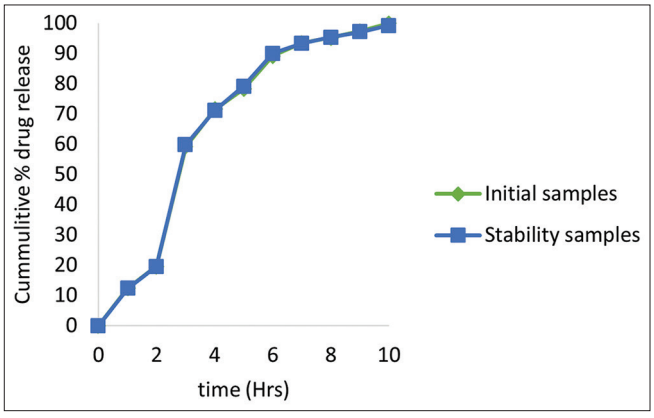

Figure 10: Assessment stability of optimized batch f5 (n = 3) drug release profiles of initial (0 day) and (after 3 months)

CONCLUSION

In house lab scale developed pastillation apparatus was successfully developed and was utilized to formulate pastilles. This is the simple technique to formulate sustained release Metformin HCl multiparticulate pastilles from solid lipids glyceryl monostearate and glyceryl monostearate a best solid lipid material for the development of sustained released pastilles of water soluble drug was evaluated successfully. Melt solidification apparatus was simple to assemble and also cost effective for small-scale development of formulation batches. The release of drug from lipid matrix by release rate modifier such as pore former was evaluated successfully. Thus, from this study it was concluded that, this is a very capable and flexible process for the formulation of oral lipid based multiparticulate sustained release formulation.

ACKNOWLEDGMENTS

All authors read and approved the manuscript. The authors are thankful for proving research facility to Faculty of Pharmacy, Bhuptal Nobles' University, old Station Road, Udaipur- 313001 Rajasthan, India.

COMPLIANCE WITH ETHICAL STANDARDS

This article does not contain any studies with human and animal subjects performed by any of the authors.

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Source of Support: Nil. **Conflicts of Interest:** None declared.