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Application of Sintering Technique for Development and *In-vitro* Characterization of Repaglinide Sustained Release Matrix Tablets

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Abstract: ***The current study attempted to develop repaglinide sustained release matrix tablets using ethyl cellulose as release retarding material. Repaglinide is an oral antihyperglycemic agentused for the treatment of Type II diabetes mellitus. Repaglinide belongs to a BCS class II drug having low solubility & high permeability. This drug was approved by FDA in 1997. Ithas half-life of 1hr. This drug is given 3-4 times per day. Due to its shorter half-life and rapid onset of action it serves as good candidate for preparing sustained release matrix tablets. Furthermore the prepared sustained release matrix tablets were subjected to chemical sintering technique, where acetone vapours were used to increase cross linkage within the polymeric structure. The tablets so designed were within the acceptable range of physicochemical properties. Formulation F10 containing ethyl cellulose, was subjected to acetone vapours up to 8 hrs has shown better dissolution profile of 93.1% in 9hrs. Hence, F10 formulation was chosen as final optimized formulation. The in-vitro release data was considered for curve fitting mathematical equations and was concluded with zero order kinetics with anomalous transport mechanism. The results lead to the conclusion thatsustained release sintered tablets of repaglinide having ethyl cellulose provides a preferable option for sustaining the drug release with low concentration of hydrophobic polymer for an extension of 9 hrs.***

Keywords: Solubility, Repaglinide, Sustained release, Ethyl cellulose

1. Introduction

A drug delivery system (DDS) is a formulation or a device that enables the introduction of therapeutic substances in to body. It is a process of administering the therapeutic substances to reach specific site of action without reaching the nontarget cells, organs ortissues in the body [1].

Drugs may be administered into the human body by different anatomical routes, either they may be intended for systemic effects or targeted to different organs and tissues. Choice of routes of administration depends upon the disease, desired effect, and availability of the product. Different routes of administration of dosage form available are: Oral, Parentral, Topical, Sublingual, Vaginal, Opthalmic, Rectal, Transdermal etc. Most preferred and common route for delivery of many of the therapeutic agents is through oral administration [2].

Oral route is a safest & most convenient route for drug administration because of more flexibility within formulation and easy for a physician during dose adjustment [3]. For long term therapy various sustained release formulations for oral route have been developed which maintain the uniform plasma drug concentration for an longer period. It enhance patient compliance and reduces the adverse side effects. Sustained release formulations are developed to release drug in pre-determined rate and able to maintained plasma drug concentration in therapeutic window with less side effects. Sustained release dosage forms have several challenges, which extend drug release, minimize the fluctuation in plasma level & minimize dosing frequency and improve drug utilization and have less side effects [3].

Generally, the sustain release tablets were develop by using high compression forces so that tablet remain intact so that it delaying the drug release. But by using such high compression forces, tablets formed will suffer from following disadvantages:

1) Drug release from harder matrix tablets may not be possible.
2) Polymorphic changes can occur at such high compression forces. Which if happens less results less stability and there by low bioavailability [3].

The above limitations may be overcome by using advanced technique called as sinteringtechnique.

Sintering entails bonding of the nearby particle surfaces in a mass of a powder or, or in a compact by the application of heat or by exposing to different solvents. This process of sintering technique can be applied for manufacturing of sustained release matrix tablets for the retarding drug release. Sintering means fusion of particles [4].

The SR dosage forms were developed by sintering the polymer matrix by employing two methods **(Figure 1):**

1) Physical Method
2) Chemical Method

1) Physical method:

It includes exposing the dosage forms to different temperatures. The polymer molecules get rearrange due to high temperature which may result in increased cross linking

in the dosage forms. This is also called as thermal sintering.

Thermal sintering: It includes exposing the solid unit dosage form to above the glass transistion temperature of the polymer Hence minute amount of polymer which present on surface melt or deform. These molecules move into the crosslinked polymer and gets entangled in the three-dimensional structure of the polymer there by increasing the complexity result in increased hardness of the dosage forms.

Limitation:
Polymers having very high melting points were not applicable for this technique. As polymer should show slight melting at sintering temperature to have rearrangement within dosage forms.

2) Chemical method
It includes exposing dosage form to different crosslinking solvents for different time points.

Acetone Saturation: Sintering technique can be applicable for punched tablets or punched tablets. The Acetone was filled in a dessicator & kept aside for saturation. After completion of saturation for 24hrs, the compressed tablets were placed over a wire-mesh which is kept above the lower chamber of the desiccator. Then the desiccator is made airtight by closing the lid with the help of wax. The acetone vapours were created in the desiccator enter the pores of tablets which solubilize the surface of the polymer matrix results in fusion of particles thus bringing about sintering. At last sintered tablets were taken out from the desiccators and kept at ambient temperature for 24hrs and stored in vaccum dessicator which was fused with calcium chloride until further use.

In most of the cases acetone is used as cross-linking solvent. These molecules are small and hence can move into the structure of the polymer where they form bonds between the particles of the polymer resulting in increased crosslinking in the polymer. Other mechanism which may involve increased cross linking is by partial solubilization.

Rearrangement -where the solvent molecules by capillary action moves in to the polymer matrix then polymer matrix gets rearrange into a more favourable packing arrangement.

Solution-Precipitation-As a result molecules in the polymer are brought to close contact with each other, which favours formation of short range welded bonds (increased cross linkage) or it favour densification, resulting in formulation with more cross linkage and with increased hardness, as cross linking directly proportional to the hardness of the pharmaceutical dosage form [5].

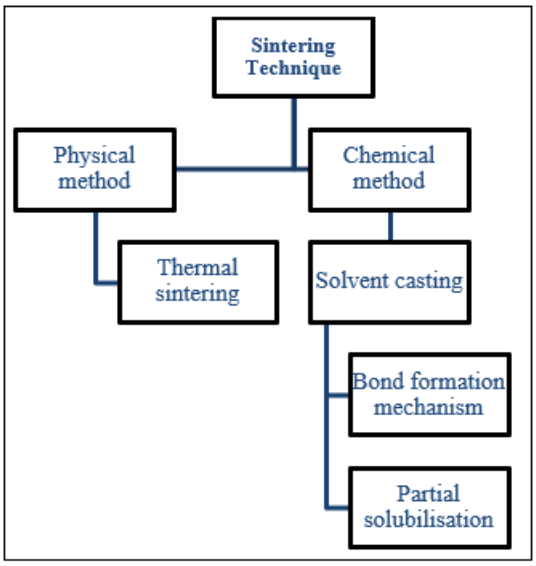


Figure 1: Classification of Sintering technique

2. Materials and Methods

Repaglinide got as gift sample from Aurobindo Pharma pvt.Ltd., Ethyl cellulose, PVP K-30, Magnesium stearate and Talc are purchased from S.D fine chemicals, India. Distilled water from in house source.

2.1 Preformulation Studies

2.1.1 Drug-excipient compatibility studies

Fourier Transform Infrared (FTIR)
The spectrum analysis of pure drug and excipients which are used for preparation of tablets was studied by FTIR. FTIR spectra were recorded using Shimadzu Corporation (Japan). KBr powder is used to prepare pellet for sampling. The scanning range was 4000$cm^{-1}$to 400 cm^{-1}

2.1.2 Flow properties

Angle of repose: Angle of repose is defined as the maximum angle possible between the surface of pile of powder and horizontal plane. It was estimated by funnel method. It was calculated using the following equation:

$$\tan \theta = h/r \text{ , } \theta = \tan^{-1} h/r \ldots\ldots \textbf{Eq 1}$$

Where, θ=angle of repose, h=height of the heap (in cm) r=radius of the base (in cm).

Bulk density: It is defined as the mass of the powder divided by the bulk volume.The bulk volume

$$b = M/V \ldots\ldots \textbf{Eq 2}$$

Tapped density: Tapped density is defined as the mass of the powder divided bythe tapped volume.

$$t = M/V \ldots\ldots \textbf{Eq 3}$$

Compressibility index: The following **equation 4** was used to obtain CI using the bulk density data that were acquired from the preceding studies.

$$\text{Carr's index} = (\text{Tapped density} - \text{Bulk density})/\text{Tapped density} \times 100 \ldots\ldots \textbf{Eq 4}$$

Hausner's ratio: It Measures the ease of powder flow in an indirect manner [6].

Hausner ratio = t/d…… **Eq 5**
Where, t=tapped density, d=bulk density

2.2 Formulation of Repaglinide Sustained Release Matrix Tablets

Preparation of Tablets: Direct compression, Wet granulation and melt granulation technique were utilized to prepare tablets.

Direct compression: Flow chart showing compression process is illustrated in **Figure 2**.

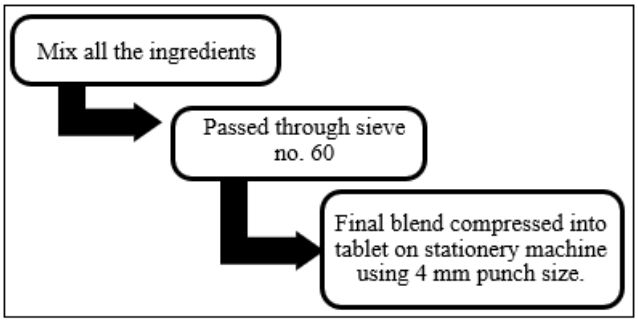


Figure 2: Flow chart showing direct compression process

Melt Granulation: Flow chart showing compression process is illustrated in **Figure 3**.

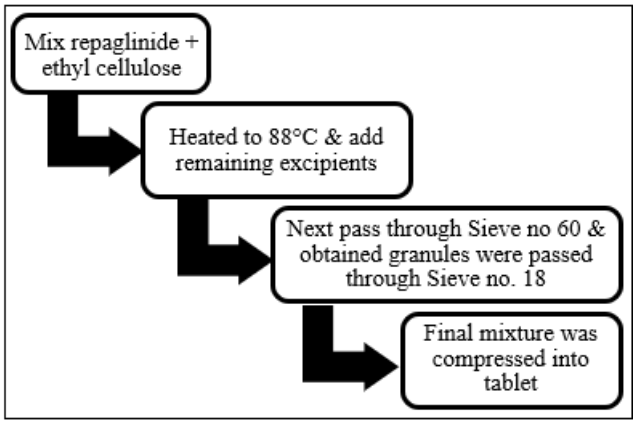


Figure 3: Flow chart showing melt granulation process

Wet Granulation: Flow chart showing compression process is illustrated in **Figure 4 [5]-[6]**.

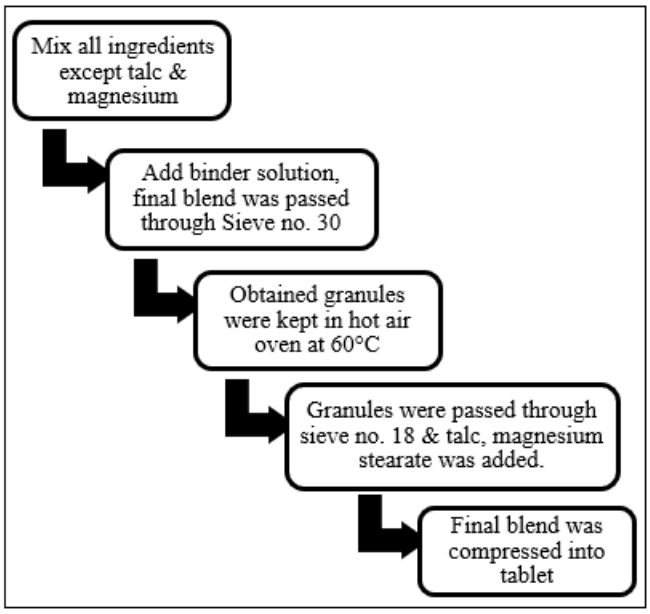


Figure 4: Flow chart showing wet granulation process

Table 1: Formulations by direct compression method

Ingredients	F9	F10	F11	F12	F13	F14
Repaglinide	8mg	8mg	8mg	8mg	8mg	8mg
HPMC K-100	16mg	-	-	-	-	8mg
Ethylcellulose	-	16mg	-	-	8mg	-
Chitosan+Gellan gum	-	-	16mg	-	-	-
K-Carrageenan+ chitosan	-	-	-	16mg	-	-
PVP K-30	1.2mg	1.2mg	1.2mg	1.2mg	0.8mg	0.8mg
Magnesium stearate	0.12mg	0.12mg	0.12mg	0.12mg	0.08mg	0.08mg
Talc	0.24mg	0.24mg	0.24mg	0.24mg	0.16mg	0.16mg
Total weight of Tablet	25mg	25mg	25mg	25mg	17mg	17mg

Table 2: Formulations by wet granulation method

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
Repaglinide	8mg	8mg	8mg	8mg	8mg	8mg	8mg	8mg
HPMC K100	8mg	-	-	-	-	-	-	-
Chitosan	-	8mg	-	-	-	-	-	-
Kondagogu gum	-	-	8mg	-	-	-	-	--
Pectin gum	-	-	-	8mg	-	-	-	-
Gellan gum	-	-	-	-	8mg	-	-	-

Locust bean gum	-	-	-	-	-	8mg	-	-
K-Carrageenan	-	-	-	-	-	-	8mg	-
PVA	-	-	-	-	-	-	-	8mg
PVP K-30	0.8mg	0.8mg	0.8mg	0.8mg	0.8mg	0.8mg	0.8mg	0.8mg
Magnesium stearate	0.08mg	0.08mg	0.08mg	0.08mg	0.08mg	0.08mg	0.08mg	0.08mg
Talc	0.16mg	0.16mg	0.16mg	0.16mg	0.16mg	0.16mg	0.16mg	0.16mg
Total weight of Tablet	17mg	17mg	17mg	17mg	17mg	17mg	17mg	17mg

Table 3: Formulations by melt granulation technique

Ingredients	F15	F16
Repaglinide	8mg	8mg
Carnauba wax	16mg	24mg
PVP K-30	1.2	1.6mg
Magnesium stearate	0.12	0.16mg
Talc	0.24	0.32mg
Total weight of tablet	25mg	34mg

2.3 Evaluation

2.3.1 Weight variation test:

20 Tablets were selected at random and were weighed from that average & Total weight was calculated. The % deviation from the average weight was calculated and shown in **Table 3** [6].

Table 3: Weight variation

Average weight	% weight variation acceptable
130 mg or less	± 10%
130-324 mg	± 7.5%
>324 mg	± 5%

2.3.2 Drug content

The average weight of 20 tablets was determined after a random selection of them.In a glass motor, tablets were ground into powder. Powder equivalent to 5mg of repaglinide was dissolved in 10ml of methanol and making volume up to the 100ml with 6.8 Phosphate buffer in 100ml volumetric flask. The supernatant was filtered. 1ml of aliquot was taken then diluted to 10ml. the solution give 10µg/ml concentration at 283.4 nm absorbance was determined against blank, with standard calibration curve, the drug content was determined [6].

2.3.3 Content uniformity

10 tablets were randomly selected from each batch. Tablets were powdered and transferred to 1000ml volumetric flask containing 10ml of methanol. Then it was well mixed by shaking the flask with 6.8 P^H buffer, volume was adjusted to the required level. The resultant solution was filtered to Whatman filter and filtered to appropriately diluted then content uniformity **[7].**

2.3.4 Thickness

Thickness can be determined by using vernier calipers [8].

2.3.5 Friability

The Roche friabilator can be used for this. Twenty tablets were weighedand placed in a Roche friabilator for 4mins at 25rpm. Tablets were reweighed after After 100 revolutions tablets should not lose more than 1% of their weight when compressed [8].

F%= (1-W0/W) × 100,

Where, W0= Initial weight of the tablet before test;

W= weight of the final tablet aftertest.

2.3.6 Hardness

The tablets tensile strength ($kg/cm^{2)}$ is used to describe its strength. The force needed to compressively break a tablet into fragments is known as" tablet crushing load". Monsanto hardness tester was used to measure it. Three tablets were randomly selected from each batch of the formulation, and the average reading was recorded [9].

2.3.7 *In-vitro* drug release

Type of apparatus: USP-II (paddle)
Vessel temperature: 37±0.5ºC
Bath temperature: 37±0.5ºC
RPM: 75rpm
Aliquot withdraw and replaced: 5ml

Sampling time intervals: 30 min, 1hr, 2hr, 3hr, 4hr, 5hr, 6hr, 7hr, 8hr up to 10hrs.

In-vitro drug release was performed using dissolution apparatus USP type II Paddle method with stirring speed of 75rpm at 37±0.5ºC in 900 ml of 6.8 phosphate buffer. The samples were collected for selected time intervals with replacement of equal volume of dissolution media. Then absorbance of selected samples was measured spectrophotometrically at 283.4nm [10].

2.3.8 Model dependent kinetics

Various kinetic models will be used to characterize the release kinetics in order to analyse the *in-vitro* release data.

Table 3: Model dependent kinetics

S. No	Mathematical model	Equation
1	Zero order	$Q_t = Q0+K0t$
2	First order	$Q_t = In\ Q0 + K1t$
3	Higuchi model	$Qt = K_H\ t^{1/2}$
4	Korsemeyer peppas model	$Qt/Q = K_k\ tn$

Where, Qt = amount of release in time; Q0 = initial amount of drug in the dosage form

Q = total amount of drug dissolved when dosage form is exhausted

K_1, K_H, K_k, k_0 = release rate constant;

n = release exponent (indicates drug release mechanism)

Table 4: Interpretation of drug release mechanism based on 'n' value

Release exponent (n)	Drug transport mechanism	Time dependent release rate
<0.5	Fickian diffusion	$t^{-0.5}$
0.5<n<1.0	Anomalous transport	t^{n-1}
1.0	Case II transport	Zero order release
Higher than 1.0	Super case II transport	t^{n-1}

2.4 Sintering Technique

Sintering entails bonding of the nearby particle surfaces in a mass of a powder or, in a compact by the application of heat or by exposing to different solvents. This process of sintering technique can be applied for manufacturing of sustained release matrix tablets for retarding drug release [11]-[12].

Procedure: Flow chart showing formulation of sintered tablets is illustrated in **Figure 5.**

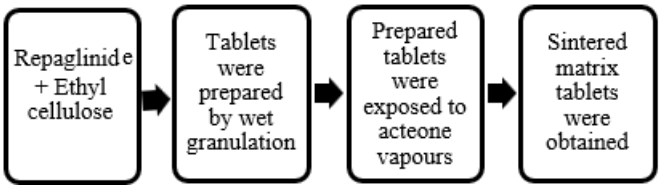


Figure 5: Formulation of ethyl cellulose sintered tablets

Formulation code	E1 (mg)	E2 (mg)
Repaglinide	8	8
Ethyl cellulose	8	16
PVPK-30	0.8	0.8
Magnesium stearate	0.08	0.08
Talc	0.16	0.16

2.5 Evaluation of sintered tablets

Prepared tablets were evaluated for different tests including hardness, friability, FTIR, and dissolution studies were conducted in 6.8 pH phosphate buffer

Model dependent method:
Optimized formulation in pH 6.8 phosphate buffer were fitted to zero, first, Higuchi and Peppas kinetics model.

FTIR studies:
Sintered tablets were crushed and powdered then it was subjected for FTIR analysis. The spectrum obtained was compared with that of pure drug.

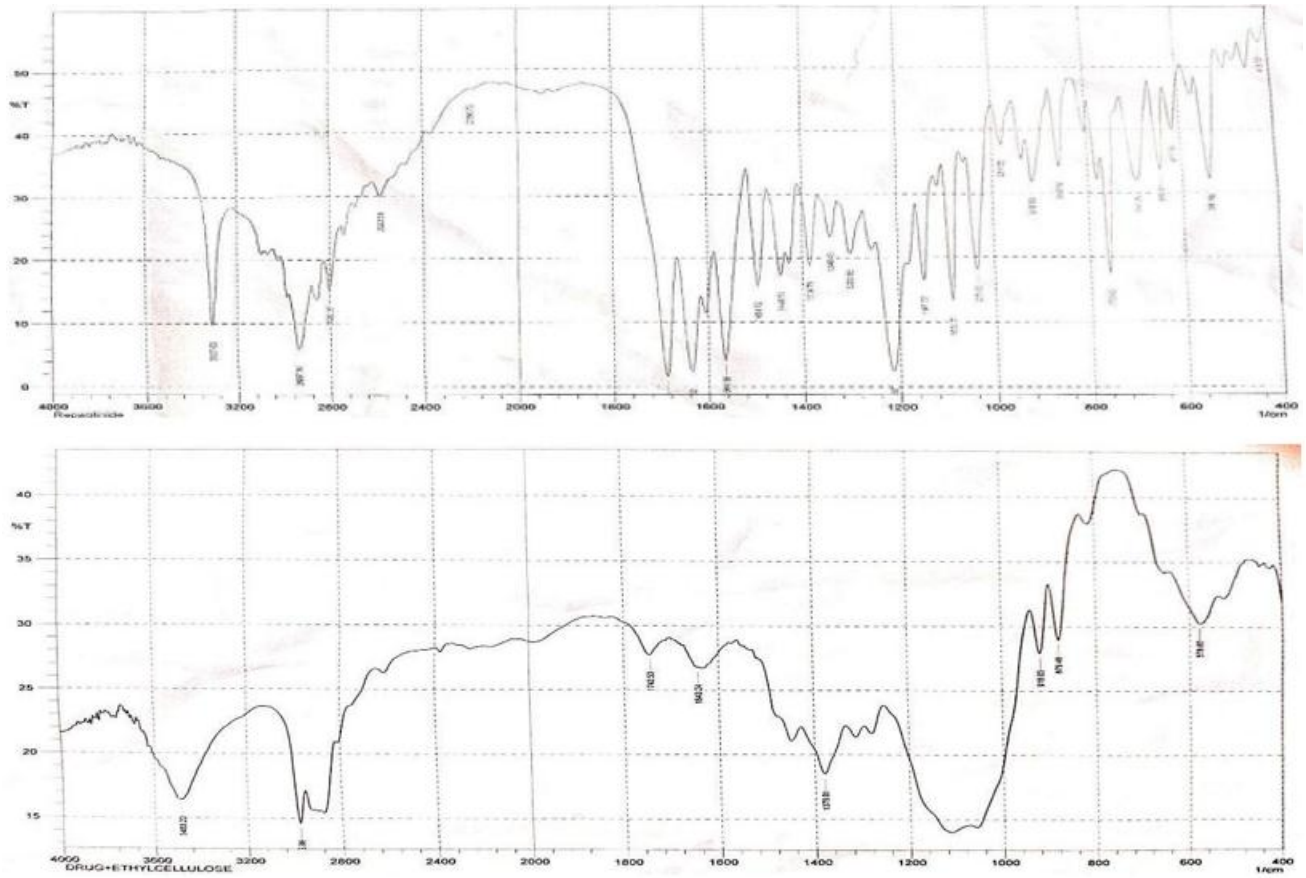
Stability studies:
Prepared tablets were carried out for stability studies according to ICH Guidelines [13].

3. Results and Discussion

3.1 Preformulation Studies

3.1.1 FTIR Studies

Repaglinide compatibility with excipients was studies by FTIR.



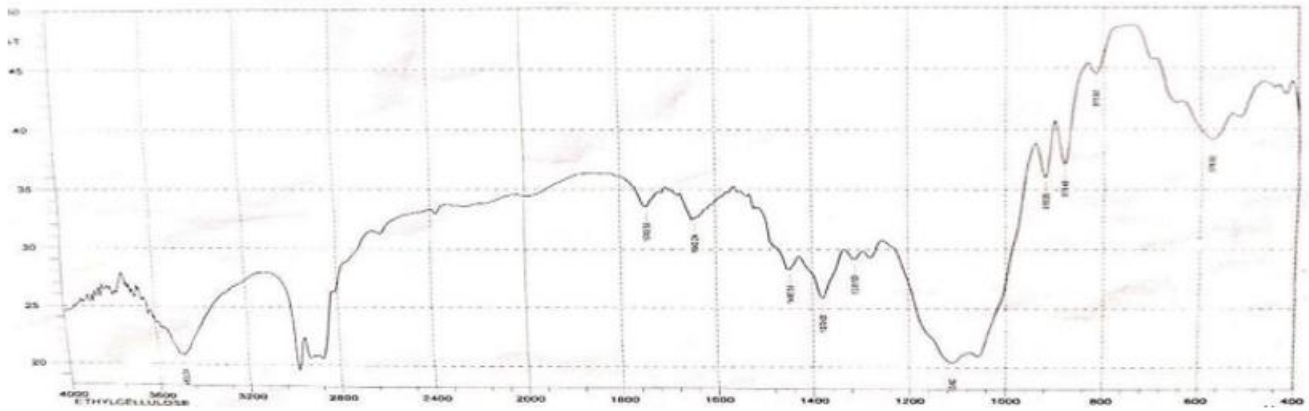
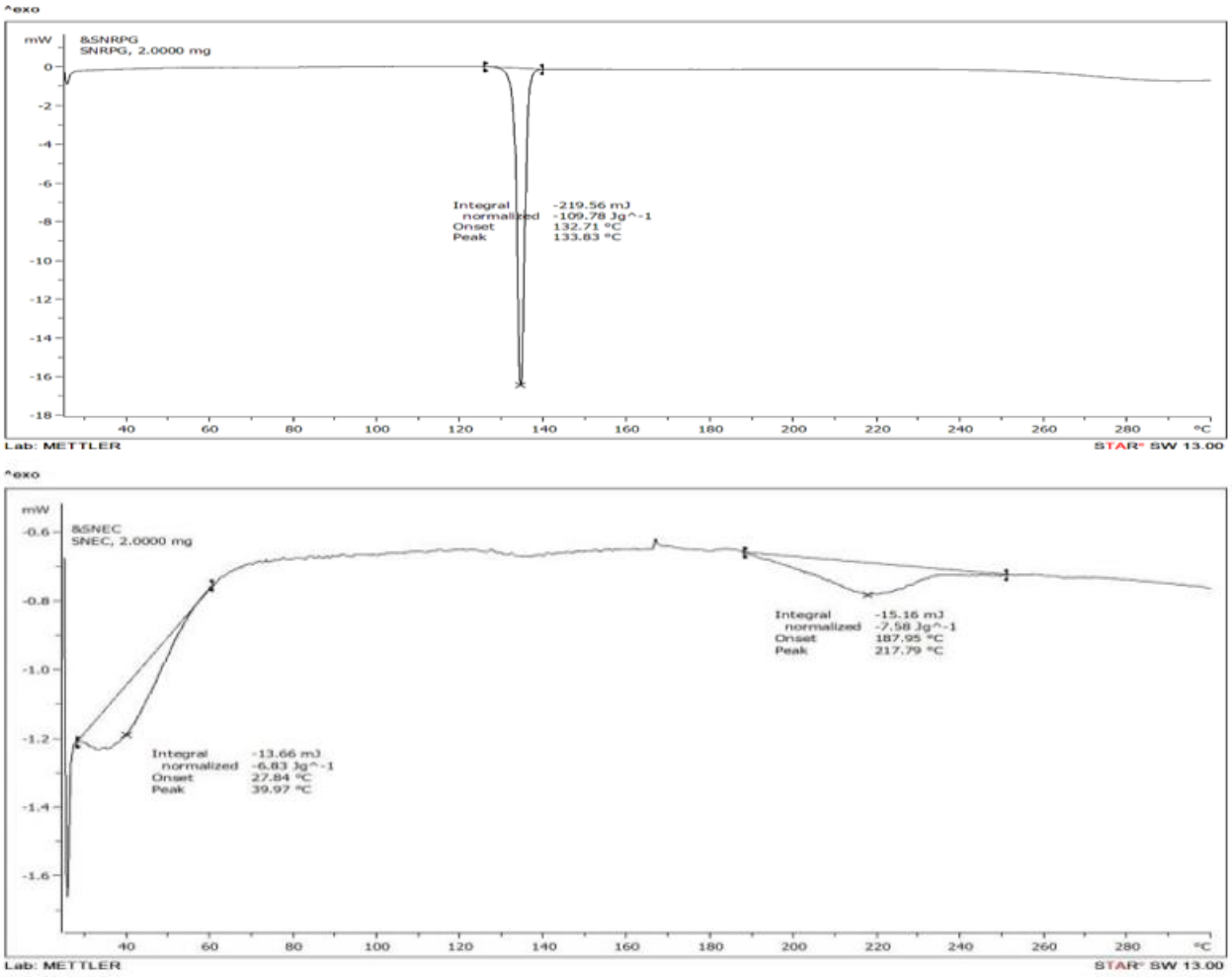
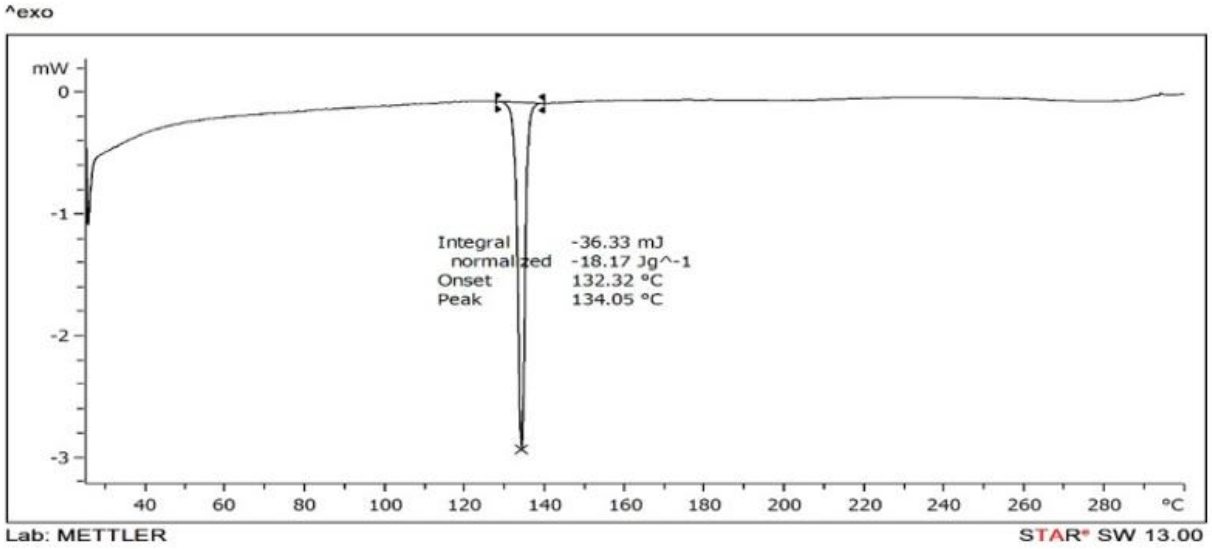


Figure 4: a) Repaglinide, b) Physical mixture of repaglinide + ethyl cellulose, c) Ethyl cellulose

3.1.2 DSC Studies





3.1.3 Evaluation of flow properties of the powder blends

The drug and other power blend did not have the required flow characteristics for directcompression. Hence tablets were made using Wet Granulation Technique.

Table 6: Precompression parameters of the powder blends

Formulation code	Angle of repose	Hausner's ratio	Carr's index	Bulk density	Tapped density
F1	53.30±0.54	1.40±0.09	29.67±0.2	0.34±0.3	0.35±0.13
F2	44.92±0.13	1.32±0.04	26.1±0.15	0.30±0.3	0.43±.25
F3	47.00±0.65	1.41±0.08	28.5±0.73	0.35±0.6	0.35±0.1
F4	50.00±0.49	1.46±0.02	27.6±0.17	0.40±0.4	0.3±0.1
F5	44.92±0.19	1.36±0.06	29.67±0.8	0.39±0.2	0.45±0.8
F6	53.30±0.45	1.45±0.04	30.1±0.10	0.30±0.2	0.54±0.8
F7	48.80±0.55	1.47±0.08	31.5±0.2	0.30±0.2	0.35±0.7
F8	52.10±0.35	1.39±0.02	37.1±0.3	0.45±0.7	0.35±0.9

Table 7: Precompression parameters of the granules

Formulation code	Angle of repose	Bulk density	Tapped density	Hausner's ratio	Carr's Index
F9	31.3±0.34	0.34±0.32	0.35±0.13	1.25±0.019	13.58±0.92
F10	28.97±0.86	0.30±0.32	0.430±.25	1.17±.022	10.10 1.52
F11	33.02±0.34	0.35±0.36	0.35±0.41	1.19±0.022	16.27±0.039
F12	37±0.10	0.40±0.24	0.3±50.31	1.22±0.001	14.2±0.29
F13	36±0.21	0.39±0.42	0.45±0.18	1.23±0.021	13.3±0.28
F14	31.3±0.34	0.30±0.32	0.54±0.28	1.26±0.019	22.16±1.20
F15	41.1±0.01	0.30±0.32	0.35±0.17	1.37±0.011	21.89±0.56
F16	32.2±0.11	0.45±0.37	0.35±0.19	1.24±0.04	22.15±1.20

3.2 Evaluation of Repaglinide Tablets

Table 8: Evaluation parameters

Formulation code	Hardness (kg/cm^2)	Thickness (mm^2)	Weight variation (%)	Friability (%)	Drug content (%)	Content uniformity
F1	2.1±0.05	3.0±0.00	0.665±0.08	0.55±0.11	97.9±0.19	92.6±0.24
F2	2.3±0.04	3.0±0.00	0.786±0.07	0.55±0.11	98.0±0.13	97.5±0.22
F3	2.4±0.03	3.1±0.9	317.16±0.76	0.76±0.09	98.0±0.13	97.5±0.22
F4	2±0.08	4±0.00	3 17.16±0.76	0.5±0.65	91±0.22	98.8±0.31
F5	2±0.07	4.1±0.09	288.33±1.52	0.51±0.3	96.8±0.10	91.6±0.28
F6	2.6±0.06	2.7±0.03	340.64±0.89	0.26±0.18	96.2±0.21	93.2±0.16
F7	2.7±0.01	2.9±0.01	310.45±1.05	0.25±0.27	97.6±0.18	98±0.24
F8	2.5±0.06	3.0±0.00	336.16±0.76	0.77±0.33	95.2±0.31	100.1±0.18
F9	2±0.01	3.5±0.05	366.33±0.65	0.55±0.11	98.0±0.13	97.5±0.22
F10	3±0.05	3.7±0.03	347.5±0.55	0.75±0.19	99±0.26	92.8±0.35
F11	2.1±0.05	2.6±0.04	317.16±0.76	0.55±0.11	98.0±0.13	97.5±0.22
F12	2±0.02	2.2±0.08	308.06±0.90	0.55±0.11	98.0±0.13	97.5±0.22
F13	2.6±0.04	2.4±0.06	317.16±0.76	0.26±0.21	97.3±0.34	92.5±0.19
F14	2.5±0.05	2.9±0.01	317.16±0.76	0.55±0.11	96.2±0.21	93.5±0.5
F15	2.5 0.06	2.8±0.02	282.88±0.83	0.55±0.11	97.6±0.18	93.2±0.16
F16	2.4 0.03	2.2±0.08	310.45±1.05	0.26±0.18	95.5±0.13	98±0.24

3.2.1 *In-vitro* dissolution studies

Table 9: Dissolution studies of F1-F8

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8
30min	26.9±0.23	21.8±0.22	29.8±0.51	18.39±0.20	19.03±0.20	26.15±0.31	37.5±0.49	33.2±0.42
1hr	35.2±0.38	48.3±0.19	33.8±0.15	39.7±0.18	31.96±0.3	44.13±0.17	59.4±0.63	57.4±0.29
2hr	62.2±0.48	65.6±0.20	45.6±0.78	63.13±0.16	51.83±0.68	60.44±0.29	68.1±0.29	76.1±0.59
3hr	78.4±0.28	80.6±0.21	65.6±0.58	78.51±0.57	69.97±0.16	75.44±0.26	76.1±0.1	83.2±0.48
4hr	82.5±0.19	90.6±0.39	80.6±0.46	83.1±0.18	89.5±0.22	89.55±0.29	90.3±0.30	91.1±0.39
5hr	92.5±0.17	95.2±0.31	90.1±0.32	91.3±0.19	96.21±0.09	93.5±0.10	91.1±0.48	100±0.32

Table 10: Dissolution studies of F9-F16

Time (min)	F9	F10	F11	F12	F13	F14	F15	F16
30min	39.1±0.11	11.12±0.03	14.9±0.55	20.1±0.75	12.1±0.21	39.1±0.39	11.12±0.55	26.15±0.5
1hr	55.3±0.23	23.1±0.12	34.9±0.17	30.1±0.88	31.16±0.31	55.3±0.19	23.1±0.62	44.3±0.22
2hr	75.1±0.11	31.5±0.22	69.1±0.76	60.1±0.19	59.1±0.65	75.1±0.30	31.5±0.30	60.44±0.52
3hr	80.1±0.21	46.7±0.23	83.4±0.58	80.1±0.55	79.1±0.19	80.1±0.33	46.7±0.11	75.44±0.45
4hr	90.1±.01	61.9±0.32	90.1±0.49	91.1±0.19	93.1±0.27	90.1±0.29	61.9±0.44	89.55±0.31
5hr	98.1±0.21	81.1±0.32	94.1±0.39	95.1±0.20	96.1±0.01	94.1±0.11	93.1±0.50	91.1±0.31

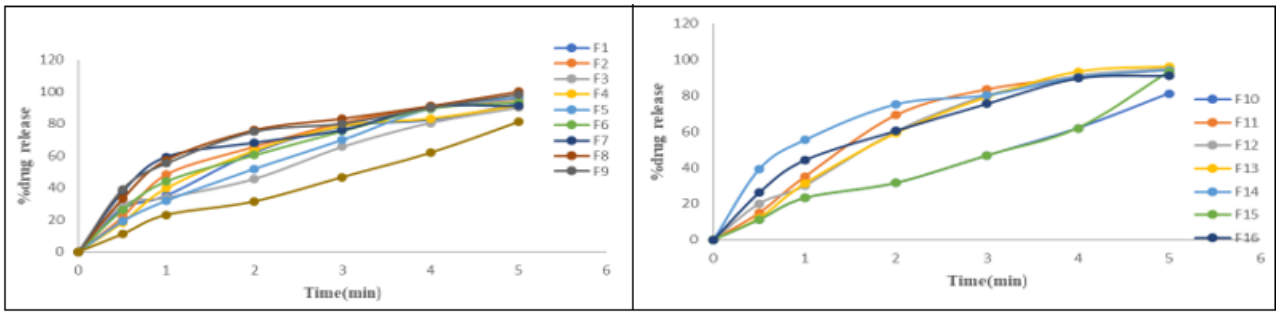


Figure 6: Dissolution profile of formulations F1-F16

Dissolution data and dissolution profiles of the formulations F1-F16 are given in **Table 9, 10 and Figure 6.**

3.2.2 Drug release kinetics: Model dependent method

Release kinetics for different formulations was calculated using Microsoft office Excel. The release data was analysed by fitting the drug release profiles of all the formulations into zero order release model, first order release model, Higuchi model and Korsmeyer Peppas model **Table 11**.

3.2.3 Sintering Technique

As mentioned before prepared tablets were subjected for acetone vapours for sintering. The main objective of sintering is to sustain the drug release with low polymeric concentration at low hardness. Hence tablets with low polymeric concentration at low hardness were prepare and subjected for sintering. Based on results on in vitro dissolution studies F10 formulation was found to be better when compared to other formulation. Hence F10 formulation subjected for sintering technique.

F10 formulation by subjecting to chemical sintering had slightly prolonged the drug release action. The reason might be due to minor increase in the polymer concentrations.

Hence based on results of dissolution studies shown in **Table 11** and **Figure 6** it can be considered that F10 on exposure of 8 hours to acetone vapours has better sustained drug release (93% in 9 hrs) compared to unsintered tablets.

Table 11: Model dependent kinetics

Formulation	Zero Order	First order	Higuchi	Korsemeyer- Peppas		Release mechanism
	R^2	R^2	R^2	R^2	N	
F1	0.934	0.979	0.9772	0.9798	0.5673	Anomalous transport
F2	0.898	0.9931	0.9648	0.9424	0.613	Anomalous transport
F3	0.989	0.9495	0.9631	0.9458	0.5078	Anomalous transport
F4	0.8985	0.9901	0.9660	0.9539	0.6792	Anomalous transport
F5	0.9821	0.9436	0.9933	0.9979	0.7182	Anomalous transport
F6	0.9509	0.9829	0.99	0.9882	0.5508	Anomalous transport
F7	0.8972	0.9526	0.9506	0.9533	0.3676	Fickian diffusion
F8	0.8803	0.8879	0.9514	0.9499	0.448	Fickian diffusion
F9	0.9251	0.91	0.9771	0.9847	0.3884	Fickian diffusion
F10	0.9892	0.9154	0.9556	0.9853	0.8132	Anomalous transport
F11	0.8682	0.9953	0.9469	0.9434	0.8049	Anomalous transport
F12	0.9341	0.9917	0.9779	0.9819	0.7247	Anomalous transport
F13	0.9293	0.9839	0.9817	0.9643	0.9033	Anomalous transport

F14	0.9003	0.9886	0.9656	0.9793	0.3785	Anomalous transport
F15	0.962	0.7609	0.9083	0973	0.8461	Anomalous transport
F16	0.9377	0.9754	0.9833	0.9845	0.544	Anomalous transport

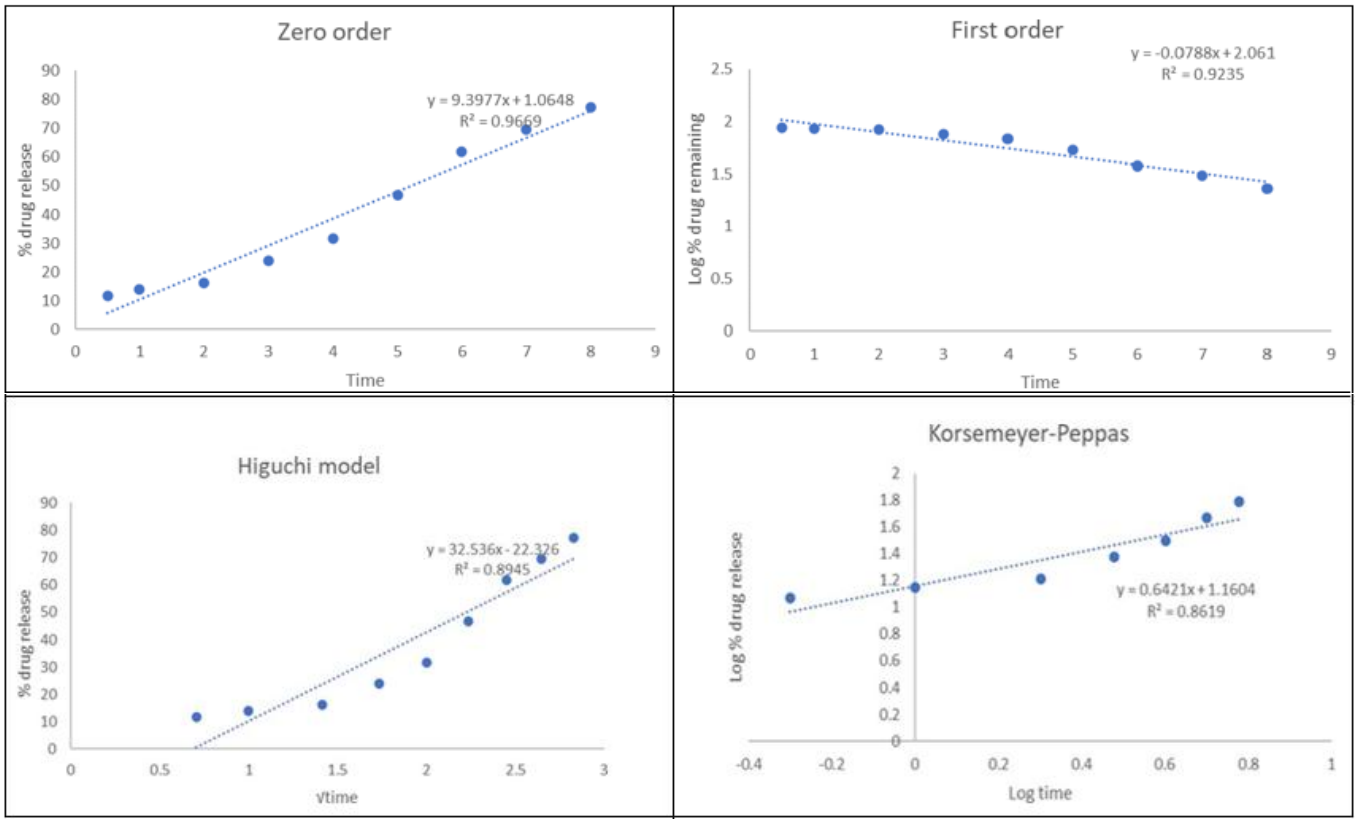


Figure 7: Model dependent kinetics of optimized formulation

3.2.4 Release kinetics of optimized formulation

Table 12: Comparison of hardness and friability of optimized formulation before and after sintering

Parameters	Before sintering	After sintering
Hardness	3±0.05	6.4±0.23
Friability	0.7%±0.19	0.5%±0.22

Table 13: Model dependent kinetics of optimized formulation

	Zero order	First order	Higuchi model	Korsemeyer-Peppas	n	Release mechanism
Optimized formulation	0.9669	0.9235	0.8945	0.8619	0.6421	Anamolous transport

Table 14: Physico-chemical properties of optimized formulation duringstability studies

Tests	0 (Initial)	1st week	2nd week	1st month
Physical Appearance	No colour change	No colour change	No colour change	No colour change
Drug content	98.3±0.38	97.6±0.69	96.5±1.06	97.5±0.73
% Drug release	77.4±0.01	76.1±0.3	78.2±0.09	77.2±0.5
Hardness	6.1±0.05	6.2±0.04	6.3±0.03	6±0.05

As mentioned, the analysis of the release data involved fitting the drug release profiles of F10 formulation (after exposure to acetone vapors for 8 hrs) into model dependent kinetics.

3.3 Stability studies

Optimized formulation was subjected for stability studies and results given in **Table 14.** Based on the results it can be concluded that, optimized tablets were stable during accelerated stability studies, with insignificant changes in the drug content, hardness and *in vitro* drug release characteristics**.**

4. Conclusion

The present study was used to extend the drug release by application of chemical sintering technique. From preliminary screening ethyl cellulose was optimized as rate retarding polymer and wet granulation technique was used in preparation of sustained release matrix tablets. The prepared tablets were subjected to sintering and evaluated for flow properties and *in-vitro* dissolution tests and they were found to be within the acceptable limits of Pharmacopeia. Among all the formulations F10 was exposed to acetone vapours for a period of 8 hrs has shown drug release up to 9 hrs. Hence it has been selected as optimized formulation. F10 was

found stable up to 3 months from the results of stability studies. Hence, among different strategies employed for the design of a sustained release dosage form, sintering technique appears to be an alternative method to sustain the drug release of repaglinide. From the study it can be concluded that using ethyl cellulose as polymer for sustaining the release of drug was found to be successful and the objective was achieved.

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