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Formulation And Evaluation Of Ganciclovir Solid Dispersions

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Abstract:
The present research work was aimed for an innovative study to explore the best among the better carriers for preparing solid dispersions (SDs) using novel microwave fusion technique by taking Ganciclovir (GCR) as model drugs. The successful carriers of Poly Ethylene Glycols (PEG-3350, PEG- 4000, PEG-6000, PEG-8000 and PEG-20000); Poly Vinyl Pyrrolidone (PVP K-12, PVP K-17, PVP K-25, PVP K-30 and PVP K-90); Poloxamers (Poloxamer 108, Poloxamer 188, Poloxamer 237, Poloxamer 338 and Poloxamer 407) and Urea were prepared as SDs by microwave induced fusion technique for increasing the solubility of GCR and LPR. Drug and carrier compatibility studies were performed. The prepared SDs were assessed for flow ability and compressed into tablets. The resulted tablets were characterized for physical parameters viz., thickness, weight uniformity, hardness, friability, uniformity in drug content, solubility and *in vitro* dissolution. The optimized formulation from GCR (combination of carrier blends) was further made a combination. A HPLC technique was established for the instantaneous assessment of the optimized combination of GCR.
Key Words: Ganciclovir, Polymer, Solid Dispersion Stability.

Introduction: The solid dosage forms (E.g., tablets, capsules) release drug instantly which are utmost used drug delivery systems (DDS). These dosage forms disintegrate and dissolve gastric fluid[1]. Dissolution of the drug(s) under physiological conditions is vital for its systemic absorption. Dissolution characterization is done for solid orals and to decide the agreement with dissolution necessities when stated in the discrete monograph.

Since the drugs selected has less solubility, there is a need to upsurge its solubility by one of the above-said methods, out of which *solid dispersion* methodology is easy, cost-effective, time-saving and more feasible.

Qualities of solid dispersions

- The drug available in SDs in solid state is helpful in stabilizing unstable drugs.
- They have rapid dissolution rate.
- They are the thermodynamically more active form of a drug and directly influences diffusion and release rate.
- The dose of the drug that is given in SDs could be decreased.

  E.g., the dose of Reserpine and Spironolactone can be reduced to half by making them as SDs.

Experimental:

Drug- Excipient Compatibility Studies:

Physical Observations of Excipients Compatibility Study at strained storage conditions:
GCR and Excipients (1:1) compatibility at stressed storage conditions was shown in table 1

Table 1: Physical Observations of Excipients Compatibility Study at stressed storage conditions

Storage condition	Binary mixture

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		temperature		**40°C/75%RH**	
	Initial	**15Days**	**30 Days**	**15 Days**	**30 Days**
GCR	White to off-white powder	NCC	NCC	NCC	NCC
GCR+PEG-3350	White waxy powder	NCC	NCC	NCC	NCC
GCR+PEG-4000	White waxy powder	NCC	NCC	NCC	NCC
GCR+PEG-6000	White waxy powder	NCC	NCC	NCC	NCC
GCR+PEG-8000	White waxy powder	NCC	NCC	NCC	NCC
GCR+PEG-20000	White waxy powder	NCC	NCC	NCC	NCC
GCR+PVP K-12	White to off-white powder	NCC	NCC	NCC	NCC
GCR+PVP K-17	White to off-white powder	NCC	NCC	NCC	NCC
GCR+PVP K-25	White to off-white powder	NCC	NCC	NCC	NCC
GCR+PVP K-30	White to off-white powder	NCC	NCC	NCC	NCC
GCR+PVP K-90	White to off-white powder	NCC	NCC	NCC	NCC
GCR+Poloxamer-108	White to off-white powder	NCC	NCC	NCC	NCC
GCR+Poloxamer-188	White to off-white	NCC	NCC	NCC	NCC

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	powder				
GCR+Poloxamer-237	White to off-white powder	NCC	NCC	NCC	NCC
GCR+Poloxamer-338	White to off-white powder	NCC	NCC	NCC	NCC
GCR+Poloxamer-407	White to off-white powder	NCC	NCC	NCC	NCC
GCR+ Urea	White to off-white powder	NCC	NCC	NCC	NCC

GCR= Ganciclovir; PEG=Poly Ethylene Glycol; PVP= Poly Vinyl Pyrrolidone; NCC= No characteristic change

Differential Scanning Calorimetry:

The DSC thermograms of GCR with PEG carrier

The DSC thermograms of Ganciclovir (GCR) with PEG carrier used was shown in figure 3 and tabulated in table 2.

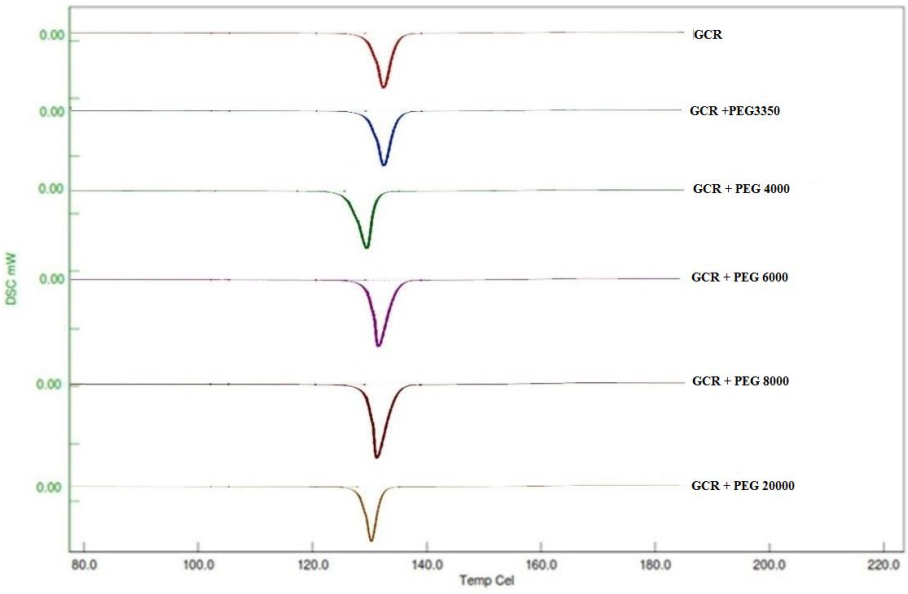

Fig.1. DSC thermograms of Ganciclovir with PEG bases

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Table 2: Endothermic events, Enthalpy and Inference of DSC data of EPEG

DSC Sample	Endothermic events (°C)			ΔH Fusion	Inference
	T onset	T Peak	Tend	Enthalpy (J)	
GCR	126.74	137.29	138.28	-156.67	An endothermic peak
GCR: PEG-3350	125.96	137.09	138.01	-149.37	A shift in peak to left due to interaction between GCR and PEG-3350
GCR: PEG-4000	123.05	131.11	135.14	-159.46	A shift in peak to left due to interaction between GCR and PEG-4000
GCR: PEG-6000	125.85	135.61	137.81	-148.91	A shift in peak to left due to interaction between GCR and PEG-6000
GCR: PEG-8000	124.95	135.09	137.99	-150.05	A shift in peak to left due to interaction between GCR and PEG-8000
GCR: PEG-20000	190.32	131.22	135.60	-152.08	A shift in peak to left due to interaction between GCR and PEG-20000

GCR- Ganciclovir; PEG-Poly Ethylene Glycol

The thermogram of GCR was characterized by single sharp endotherm at 137.29ºC (indicates its melting). The DSC thermogram of the drug was observed to be in contract with the specifications.

GCR-PEG bases thermograms were also produced single endothermic peaks at 137.09ºC, 131.11ºC, 135.61ºC, 135.09ºC and 131.22ºC for GCR when combined (by microwave induced fusion) with PEG-3350, PEG-4000, PEG-6000, PEG-8000 and PEG-20000 respectively. These thermograms indicated that a little shift towards left when combined with PEG carriers may be due to the dissolution of GCR/mixing/its conversion into amorphous form. These thermograms indicate no sign of drug- excipients incompatibility of GCR with PEG carriers used.

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The DSC thermograms of GCR with PVP carrier

The DSC thermograms of GCR with PVP carrier used was shown in figure 4 and tabulated in table 3.

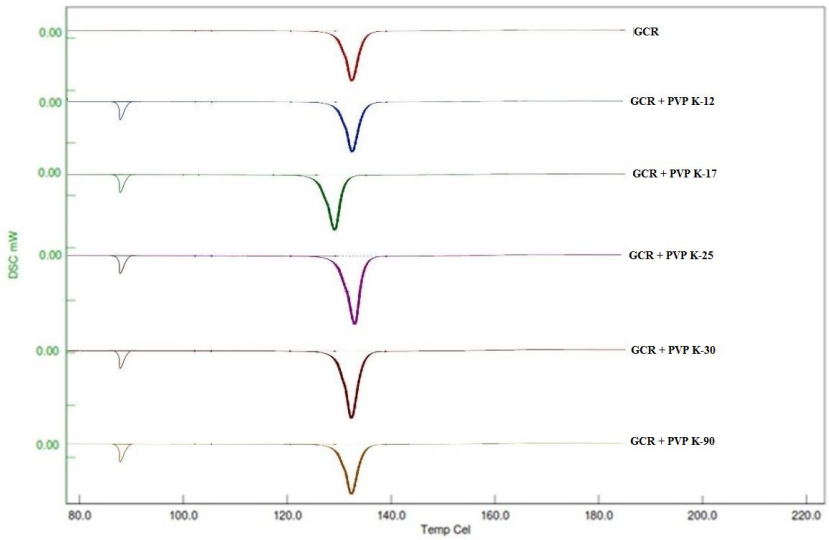

Fig.2. DSC thermograms of Ganciclovir with PVP bases

Table 3: Endothermic events, Enthalpy and Inference of DSC data of EPVP

DSC	Endothermic events (°C)			ΔH Fusion	Inference
Sample	T onset	T peak	Tend	Enthalpy (J)	
GCR	126.74	137.29	138.28	-156.67	An endothermic peak
GCR: PVP K-12	125.96	136.52	138.95	-150.49	A shift in peak to left due to interaction between GCR and PVP K-12
GCR: PVP K-17	120.05	130.09	134.71	-157.51	A shift in peak to left due to interaction between GCR and PVP K-17
GCR: PVP K-25	126.17	134.33	137.02	-148.66	A shift in peak to left due to interaction between GCR and PVP K-25

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GCR: PVP K-30	124.95	134.88	137.04	-151.44	A shift in peak to left due to interaction between GCR and PVP K-30
GCR: PVP K-90	123.15	133.82	135.11	-151.52	A shift in peak to left due to interaction between GCR and PVP K-90

GCR- Ganciclovir; PVP-Poly Vinyl Pyrrolidone

GCR-PVP bases thermograms were also produced single endothermic peaks at 136.52ºC, 130.09ºC, 134.33ºC, 134.88ºC and 133.82ºC for GCR when combined (by microwave induced fusion) with PVP K-12, PVP K-17, PVP K-25, PVP K-30 and PVP K-90 respectively. These thermograms indicated that a little shift towards the lower temperature when combined with PVP carriers, this may be due to the dissolution of GCR/mixing/its conversion into amorphous form. These thermograms indicate no sign of drug-excipients incompatibility of GCR with PVP carriers used.

The DSC thermograms of GCR with Poloxamer carrier

The DSC thermograms of GCR with Poloxamer carrier used was shown in figure 3 and tabulated in table 4.

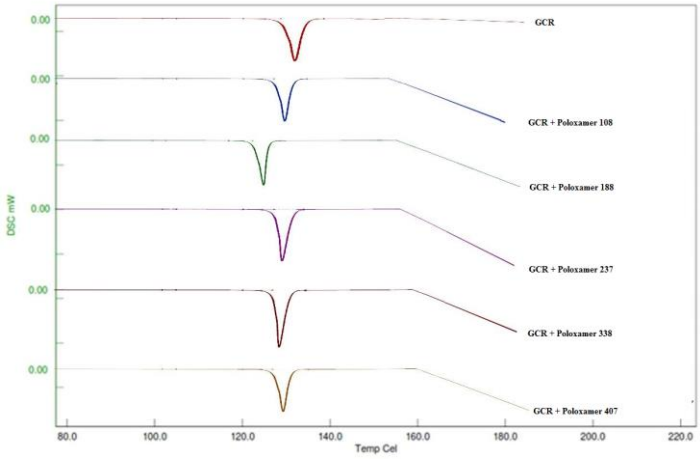

Fig.3. DSC thermograms of Ganciclovir with Poloxamer bases

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Table 4: Endothermic events, Enthalpy and Inference of DSC data of EP

DSC sample	Endothermic events (°C)			ΔH Fusion	Inference
	T onset	T peak	Tend	Enthalpy (J)	
GCR	126.74	137.29	138.28	-156.67	An endothermic peak
GCR:P108	120.86	129.30	134.12	-146.22	A shift in peak to left due to interaction between GCR and Poloxamer P-108
GCR:P188	121.06	125.19	131.65	-135.16	A shift in peak to left due to interaction between GCR and Poloxamer P-188
GCR:P237	119.98	128.01	133.26	-146.28	A shift in peak to left due to interaction between GCR and Poloxamer P-237
GCR:P338	120.23	129.62	134.15	-152.79	A shift in peak to left due to interaction between GCR and Poloxamer P-338
GCR:P407	122.99	133.75	134.16	-151.29	A shift in peak to left due to interaction between GCR and Poloxamer P-407

GCR- Ganciclovir; P-Poloxamer

GCR-Poloxamer bases thermograms were also produced single endothermic peaks at 129.30ºC, 125.19ºC, 128.01ºC, 129.62ºC and 133.75ºC for GCR when combined (by microwave melting) with Poloxamer-108, Poloxamer-188, Poloxamer- 237, Poloxamer-338 and Poloxamer-407 respectively. These thermograms indicated that a little shift towards the lower temperature when combined with Poloxamer carriers, because of the dissolution of GCR/mixing/its conversion into amorphous form. These thermograms indicate that there is no sign of drug-excipients incompatibility of GCR with Poloxamer carriers used.

The DSC thermograms of GCR with Urea carrier

The DSC thermograms of GCR with Urea carrier used was shown in figure 4 and tabulated in table 5.

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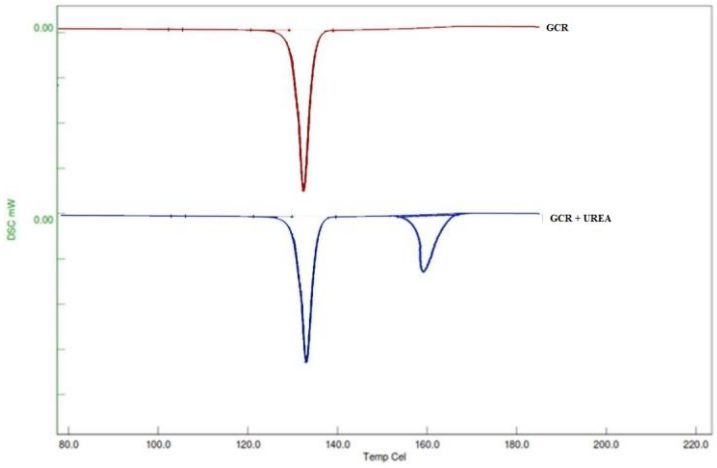

Fig.4. DSC thermograms of Ganciclovir with Urea

Table 5: Endothermic events, Enthalpy and Inference of DSC data of EU

	Endothermic events (°C)			ΔH Fusion	
DSC sample	**T onset**	**T peak**	**Tend**	**Enthalpy (J)**	**Inference**
GCR	126.74	137.29	138.28	-156.67	An endothermic peak
GCR: U	125.69	136.98	137.29	-151.39	A shift in peak to left due to interaction between GCR and Urea

GCR- Ganciclovir; U-Urea

GCR-Urea bases thermograms were also produced single endothermic peaks at 136.98^{o}C for GCR when combined (by microwave melting) with Urea. These thermograms indicated that a little shift towards the lower temperature when combined with Poloxamer carriers, because the dissolution of GCR/mixing/its conversion into amorphous form. These thermograms indicate that there is no sign of drug-excipients incompatibility of GCR with Urea.

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Results of pre-compression parameters

Flow properties (Pre Compression)

The prepared GCR SDs when checked for flow characteristics which were represented in table 6 to 8.

Table 6: Flow character specifications (Ganciclovir+ PEG)

Formulation	Flow properties				
	Angle of repose (^{0})	**Bulk Density**	**Tapped Density**	**Carr's Index**	**Hausner Ratio**
EPEG3-1	25.21±0.04	0.401±0.02	0.450±0.02	10.889±0.01	1.122±0.06
EPEG3-2	29.33±0.05	0.400±0.03	0.416±0.02	3.846±0.02	1.040±0.02
EPEG3-3	34.21±0.04	0.377±0.01	0.403±0.02	6.451±0.05	1.068±0.07
EPEG3-4	25.21±0.02	0.393±0.02	0.422±0.03	6.872±0.09	1.073±0.06
EPEG4-1	26.33±0.01	0.412±0.03	0.445±0.02	7.415±0.04	1.080±0.02
EPEG4-2	28.45±0.08	0.402±0.02	0.462±0.03	12.987±0.08	1.149±0.06
EPEG4-3	29.21±0.09	0.502±0.01	0.526±0.02	4.562±0.03	1.047±0.02
EPEG4-4	29.04±0.06	0.195±0.05	0.203±0.02	3.940±0.02	1.041±0.03
EPEG6-1	30.25±0.04	0.252±0.02	0.269±0.01	6.319±0.05	1.067±0.06
EPEG6-2	29.21±0.01	0.393±0.08	0.425±0.03	7.529±0.03	1.081±0.02
EPEG6-3	27.25±0.03	0.323±0.02	0.352±0.02	8.238±0.07	1.089±0.05
EPEG6-4	25.09±0.02	0.512±0.04	0.548±0.05	6.569±0.03	1.070±0.02
EPEG8-1	27.27±0.05	0.623±0.02	0.666±0.02	6.456±0.05	1.069±0.06
EPEG8-2	26.21±0.04	0.854±0.05	0.898±0.03	4.899±0.03	1.051±0.04
EPEG8-3	26.37±0.09	0.269±0.01	0.279±0.01	3.584±0.02	1.037±0.06
EPEG8-4	31.21±0.04	0.562±0.03	0.587±0.06	4.258±0.01	1.044±0.06
EPEG20-1	30.54±0.06	0.348±0.02	0.358±0.02	2.793±0.08	1.028±0.05
EPEG20-2	28.45±0.02	0.365±0.02	0.375±0.04	2.666±0.09	1.027±0.06
EPEG20-3	29.35±0.04	0.848±0.03	0.878±0.01	3.416±0.03	1.035±0.08
EPEG20-4	27.97±0.05	0.458±0.01	0.512±0.03	10.546±0.02	1.117±0.02

Values in mean ±SD; trials made (n=3)

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Table 7: Flow character specifications (Ganciclovir+ Poloxamer)

Formulation	Flow properties				
	Angle of repose (^{0})	**Bulk Density**	**Tapped Density**	**Carr's Index**	**Hausner Ratio**
EP108-1	30.50±0.06	0.235±0.01	0.255±0.03	7.843±0.06	1.085±0.01
EP108-2	28.77±0.04	0.456±0.03	0.468±0.03	2.564±0.01	1.026±0.02
EP108-3	25.71±0.06	0.856±0.05	0.879±0.01	2.616±0.03	1.027±0.09
EP108-4	29.48±0.05	0.759±0.02	0.779±0.02	2.567±0.06	1.026±0.03
EP188-1	26.39±0.02	0.958±0.01	0.977±0.01	1.944±0.01	1.019±0.03
EP188-2	33.36±0.06	0.658±0.04	0.689±0.01	4.499±0.02	1.047±0.05
EP188-3	30.11±0.11	0.842±0.05	0.874±0.02	3.661±0.03	1.038±0.01
EP188-4	28.52±0.13	0.758±0.03	0.769±0.06	1.430±0.01	1.014±0.08
EP237-1	29.33±0.08	0.526±0.02	0.536±0.04	1.866±0.03	1.019±0.03
EP237-2	33.45±0.09	0.365±0.09	0.384±0.02	4.947±0.04	1.052±0.02
EP237-3	29.48±0.03	0.445±0.03	0.457±0.01	2.583±0.03	1.026±0.01
EP237-4	26.32±0.02	0.521±0.04	0.530±0.04	1.698±0.01	1.017±0.03
EP338-1	27.09±0.06	0.656±0.03	0.666±0.03	1.501±0.05	1.015±0.02
EP338-2	26.37±0.14	0.625±0.05	0.643±0.03	2.799±0.03	1.028±0.03
EP338-3	33.23±0.01	0.635±0.03	0.701±0.03	9.415±0.01	1.104±0.03
EP338-4	30.55±0.08	0.528±0.01	0.584±0.01	9.589±0.07	1.106±0.01
EP407-1	29.42±0.02	0.659±0.03	0.695±0.03	5.179±0.04	1.055±0.02
EP407-2	32.37±0.08	0.458±0.02	0.487±0.01	5.955±0.01	1.063±0.02
EP407-3	30.58±0.09	0.689±0.03	0.712±0.03	3.230±0.03	1.033±0.06
EP407-4	25.99±0.03	0.758±0.03	0.789±0.02	3.929±0.01	1.041±0.03

Values in mean ±SD; trials made (n=3)

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Table 8: Flow character specifications (Ganciclovir+ Urea)

Flow Properties					
Formulation	**Angle of repose (0)**	**Bulk Density**	**Tapped Density**	**Carr's Index**	**Hausner Ratio**
EU-1	29.52±0.03	0.584±0.08	0.597±0.03	2.177±0.03	1.022±0.01
EU-2	26.16±0.08	0.295±0.03	0.325±0.02	9.230±0.05	1.102±0.06
EU-3	29.84±0.02	0.359±0.02	0.398±0.01	9.799±0.08	1.109±0.02
EU-4	29.65±0.09	0.985±0.07	1.020±0.02	3.431±0.04	1.035±0.01

Values in mean ±SD; trials made (n=3)

Micromeritic properties (viz., the angle of repose, bulk density, tapped density, Carr's index and Hausner ratio) of prepared SDs (GCR SDs with PEG, PVP, Poloxamer and Urea bases) were evaluated before compression. The results of the angle of repose were found to be 25-30^{o} designates excellent flow characteristics. The compressibility index values were found up to 15%, this indicates in good to excellent flow properties. Additionally, the dispersions showed a Hausner ratio less than 1.25 is an indication of good flowability.

The solid dispersions were compressed into tablets and the parameters evaluated were as follows.

The tablets of different SDs were subjected to various evaluation tests such as uniformity of weight, hardness, thickness, friability, yield and assay. The results showed almost uniform thickness in all the formulations. In a weight variation test, the pharmacopoeial limit is ± 5% (for 250 mg tablet). The average percent deviation of all tablet formulations was found to be within the above limit; hence all the formulations passed the uniformity of weight as per official requirements. All the tablets were found to have sufficient strength or hardness (>4Kg/cm^2). Tablet hardness is not an absolute indicator of strength, so friability was also conducted and the loss on friability was less than 1% in all formulations (acceptable limit). Good uniformity in drug content was found among different batches of tablets and the percentage of drug content was more than 95%. The % yield was also more than 95% in all the formulations.

The practical yield among GCR-PEG SDs was found maximum for EPEG3-4 formulation; among GCR-PVP SDs the maximum yield was found in EPVP25-1 formulation; among GCR-Poloxamer SDs the maximum yield was found in EP188-4 formulation; among GCR-Urea SDs the maximum yield was found in EU-2 formulation.

Summary and Conclusion:

The majority of drugs are of poor water soluble and such compounds may exhibit insufficient dissolution throughout the gastrointestinal tract results in failing to achieve systemic acquaintance after oral administration. Fading bioavailability is the major cause for leaving inventive oral dosage forms. The applicability of the solid dispersion technique as an approach for improving the gastric absorption of drugs has been discovered in order to attain better dissolution characteristics and better bioavailability for

poorly soluble drugs.

The thermograms of GCR showed their dissolution/mixing/its alteration into amorphous form and showed no sign of incompatibility with carriers used.

The presence of distinctive peaks and stretches in FTIR spectra of GCR was also found even in their blends with SDs carriers used indicates no negative chemical interaction carriers with drugs.

The *in vitro* release data revealed that the GCR SDs with 1:6 ratio of GCR and PEG i.e., formulations EPEG3-4, EPEG4-4, EPEG6-4, EPEG8-4 and EPEG20-4 showed the rapid and higher dissolution of GCR when linked to GCR pure drug.

The *in vitro* release data revealed that GCR SDs with 1:6 ratio of GCR and PVP i.e., formulations EPVP12-4, EPVP17-4, EPVP25-4, EPVP30-4 and EPVP90-4 showed the rapid and higher dissolution of GCR when associated to GCR pure drug.
The *in vitro* release data revealed that GCR SDs with 1:6 ratio of GCR and Poloxamer i.e., formulations EP108-4, EP188-4, EP237-4, EP338-4 and EP407-4 showed the rapid and higher dissolution of GCR when matched to GCR pure drug.

The *in vitro* release data revealed that GCR SDs with 1:6 ratio of GCR and Urea i.e., formulation EU-4 showed fast and higher dissolution of GCR when likened to GCR pure drug.

GCR SDs with PEG-8000, PVP K-25, Poloxamer-188 and Urea showed good physicochemical properties, solubility profile and release rate characteristics. The optimized formulations were prepared with the combination of these carriers (PEG- 8000+PVP K-25+Poloxamer 188+Urea). The SDs formulations containing GCR were named as E-1, E-2, E-3, E-4, E-5 and E-6.

The optimized SDs of GCR (E-1 to E-6) showed excellent flow properties.

The optimized SDs tablets (E-1 to E-6) were found to have uniformity of weight and thickness. These formulations passed the hardness and friability. The percentage of drug content and yield were found to be good.

Among the optimized GCR SDs (E-1 to E-6), formulation E-6 showed 15.18 times more solubility compared to GCR alone in the water.

Amongst optimized GCR SDs (E-6) showed well *in vitro* release profile related to GCR: individual carrier combination.

CONFLICTS OF INTEREST: NIL

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