

Improvement of Solubility of Repaglinide by Physical Mixing and Melt Solvent Method

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Abstract: This study focused on an investigation of solubility and dissolution rate of the drug repaglinide, a practically water-insoluble antidiabetic drug and the purpose of this study was to enhance the dissolution rate by solid dispersion system consisting of drug, excipients and carrier. Solid dispersion formulations were prepared by using the physical mixing and melt Solvent method. Physical mixtures (PMs) of repaglinide and hydrophilic polymer Kollicoat IR, HPMC, Kollidon 90F, Poloxamar 407 and PVK 30 were prepared at 1:1, 1:3 and 1:5 ratios. Melt Solvent method was used to prepare solid dispersion of repaglinide with hydrophilic excipients Kollicoat IR, HPMC, Kollidon 90F, Poloxamar 407 and PVK 30 at 1:1, 1:3 and 1:5 ratios. All formulations were characterized by scanning electron microscopy (SEM) and dissolution tests. Characterization studies revealed that solid dispersion prepared by melt solvent methods showed better dissolution property compared to physical mixing and pure repaglinide due to the conversion into a less crystalline and/or amorphous form. The order of dissolution enhancement was Kollicoat IR > PVK30 > Kollidon 90F > Poloxamar 407 > HPMC in solid dispersions. In all cases improvement of dissolution was significantly greater in solid dispersions prepared by Melt solvent method than in physical mixtures. The SEM studies influenced that a decreased crystallinity of the solid dispersions revealed that a portion of repaglinide was in an amorphous state. This was because of Kollicoat IR, Kollidon 90F, Poloxamar 407, HPMC and PVK 30 modified the crystallinity that could be considered as an important factor in enhancement of the dissolution rate.

Keywords: Melt Solvent method; Repaglinide; hydrophilic excipients; poorly water-soluble drug; dissolution rate.

INTRODUCTION

Repaglinide is a water insoluble antidiabetic drug which belongs to the class of medications known as meglitinides [1]. It lowers the blood glucose by stimulating the release of insulin from the pancreatic β -cell [2-4]. Repaglinide is a poorly water-soluble approximately 20 $\mu\text{g}/\text{mL}$, high lipophilicity and relatively low oral bioavailability (56 %) which is attributed to poor dissolution (BCS class II) and however once it dissolved can be absorbed rapidly and completely in the gastrointestinal tract [5,6].

Repaglinide has very low and erratic bioavailability due to its lower water solubility. Therefore, it is essential to design effective methods to boost their dissolution, hence their oral absorption which will increase bioavailability. The enhancement of bioavailability of poorly soluble drugs in oral route remains one of the most challenging aspects of formulation development [7]. Though salts formation, micronization, particle size reduction and solubilization have commonly been used to raise dissolution rate and thereby oral absorption and bioavailability of such

drugs, there are some practical drawbacks of these techniques [8]. Solid dispersions have been considered as an effective method for enhancing drug dissolution rate and saturation solubility in the gastrointestinal fluids [9]. Solid dispersion (SD) is defined as the dispersion of one or more active ingredients in inert carriers at solid state prepared by melt Solvent or solvent melt methods [10, 11]. Solid dispersion system provides the possibility of reducing the particle size and modifying the drug crystal structure to the shapeless amorphous state, and/or to locally increase the saturation solubility [12, 13].

Solid dispersion formulations of a poorly soluble drug have been prepared by mixing with hydrophilic polymers is a promising method for improving the dissolution characteristics and bioavailability of the drug [14, 15]. Water-soluble carriers such as polyvinylpyrrolidone [16, 17], mannitol, poloxamer [18], hydroxypropyl methylcellulose [19] and polyethylene glycols etc. have been employed for preparing solid dispersions of different drugs to improve dissolution rate. In the

current research, an effort has been made to increase solubility of repaglinide by solid dispersion using physical mixing (PM) and melt Solvent technique using a series of hydrophilic excipients Kollicoat IR, Kollidon 90F, Poloxamar 407, HPMC and PVK 30.

MATERIALS AND METHODS

Materials

Repaglinide, Kollicoat IR and Kollidon 90F was provided as generous gift from Beximco Pharmaceutical, Bangladesh (Analytical grade). Poloxamar 407, HPMC and PVK 30 were obtained from BASF (Germany). All other materials and reagents were of analytical grade of purity.

Preparation of Physical Binary Mixtures of Repaglinide -polymer

Physical mixtures of repaglinide with Poloxamar 407, Kollicoat IR, Kollidon 90F, HPMC and PVK 30 were prepared by mixing in a mortar and pestle for 20 minutes. The binary mixtures of drug-polymers were then stored in desiccators at a room temperature until further test and were letter-coded as PM (physical mixture) (Table-1).

Preparation of Solid Dispersion by Melt Solvent Method:

Polyethylene glycol 6000 was accurately weighed and placed in an aluminum pan on a hot plate and melted at a temperature around 55°-60° C. Then accurately weighed repaglinide & polymer were added in the molten PEG with continuous stirring to assure homogenous mixing. The mixtures were then allowed to cool-down to room temperature to get the dry and solid mass of the mixtures. The ternary mixtures were then pulverized in a mortar-pestle and sieved through a 30-mesh sieve to have solid-dispersion (SD) powders of uniform-size. The SD powders were then preserved in desiccator at the ambient temperature for further use. SD powders were letter-coded as MS (melt-solvent) (Table-1).

Scanning Electron Microscopy (SEM)

The scanning electron microscopy (SEM) analysis was carried out using scanning electron microscope (JSM 6100, Jeol, Japan). Samples of Pure repaglinide, physical mixtures formulations and solid dispersion were mounted onto the stubs using double-sided adhesive tape and then coated with a thin layer of gold palladium alloy (150–200Å^o). The scanning electron microscope was operated at an acceleration voltage of 20 KV, working distance (12–14 mm). The selected magnification was ×500. SEM was used to investigate particle shape of formulations [20].

In vitro release studies

In vitro dissolution studies of pure drug, PM, and SD formulations equivalent to 2 mg of repaglinide were performed in USP type II paddle type apparatus (ELECTRO LAB, India) using 900 mL distilled water maintaining at 37 ± 0.5° C as dissolution medium and 50 rpm as the paddle rotation speed. Each time, 10 mL of dissolution medium was withdrawn at predetermined time intervals and 10 mL fresh distilled water was added immediately to maintain the sink condition. The withdrawn dissolution medium samples were filtered through 0.45 m filter paper and analyzed for drug content by a UV-VIS (Varian Cary 5000 or Agilent Cary 60) spectrophotometers at a of 243 nm.

RESULTS AND DISCUSSION

Scanning Electron Microscopy (SEM)

SEM studied indicated that pure drug repaglinide particles were irregular in shape, while the physical mixture of the drug and hydrophilic excipients show that drug particle remains dispersed and physically adsorbed on the surface of the carrier particles. The solid dispersion of repaglinide, Poloxamar 407, Kollicoat IR, Kollidon 90F, HPMC and PVK 30 showed a homogeneous dispersion indicating that the repaglinide molecules were dispersed uniformly in carrier of solid dispersion prepared by melting method at 1:5 ratios, assuming modified to amorphous.

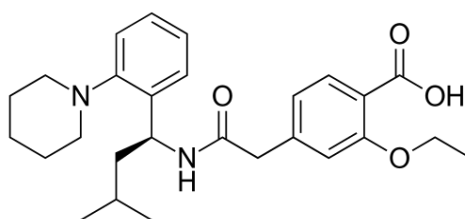


Fig-1: Chemical structure of repaglinide [4]

Table-1: Different Formulations Prepared by Physical Mixing and Melt Solvent Method

S. No.	Polymer	Formulation Combination		Assigned Code of the formulated batches	
		Physical Mixing (RpG: P)	Melt Solvent Method (C: RpG :P)		
1	Kollicoat IR	1:1	5:1:1	PM ₁	MS ₁
2		1:3	5:1:3	PM ₂	MS ₂
3		1:5	5:1:5	PM ₃	MS ₃
4	PVP K30	1:1	5:1:1	PM ₄	MS ₄
5		1:3	5:1:3	PM ₅	MS ₅
6		1:5	5:1:5	PM ₆	MS ₆
7	Poloxamar 407	1:1	5:1:1	PM ₇	MS ₇
8		1:3	5:1:3	PM ₈	MS ₈
9		1:5	5:1:5	PM ₉	MS ₉
10	Kollidon 90F	1:1	5:1:1	PM ₁₀	MS ₁₀
11		1:3	5:1:3	PM ₁₁	MS ₁₁
12		1:5	5:1:5	PM ₁₂	MS ₁₂
13	HPMC	1:1	5:1:1	PM ₁₃	MS ₁₃
14		1:3	5:1:3	PM ₁₄	MS ₁₄
15		1:5	5:1:5	PM ₁₅	MS ₁₅

RpG = Repaglinide; P = polymer; C = Carrier, PEG 6000; PM = physical mixing; MS = melt-solvent

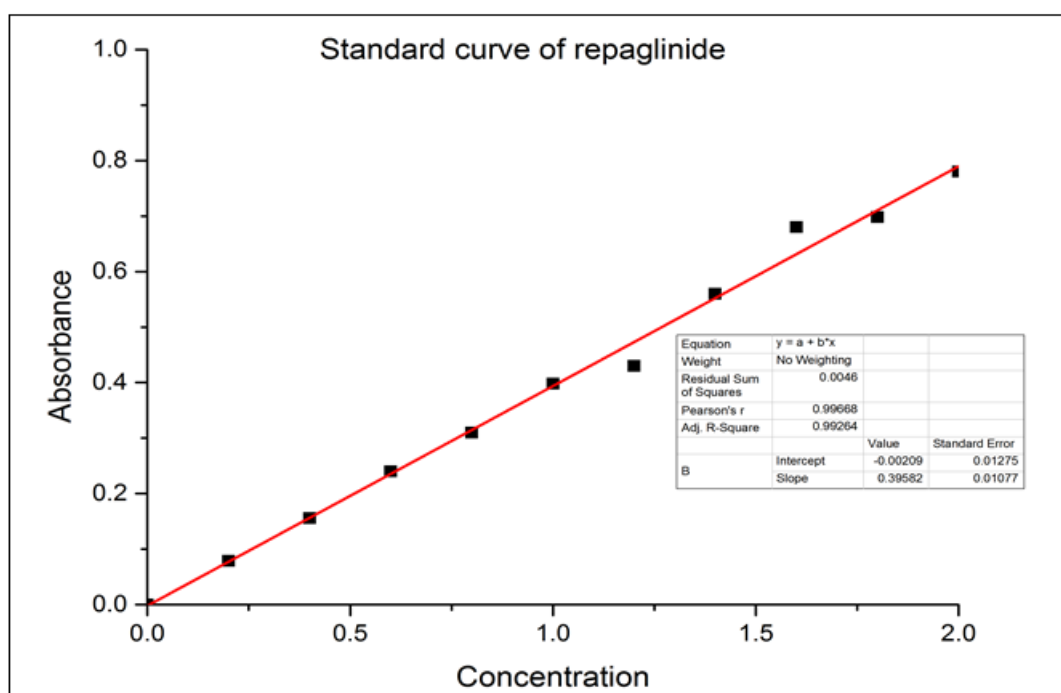


Fig-2: standard curve of repaglinide

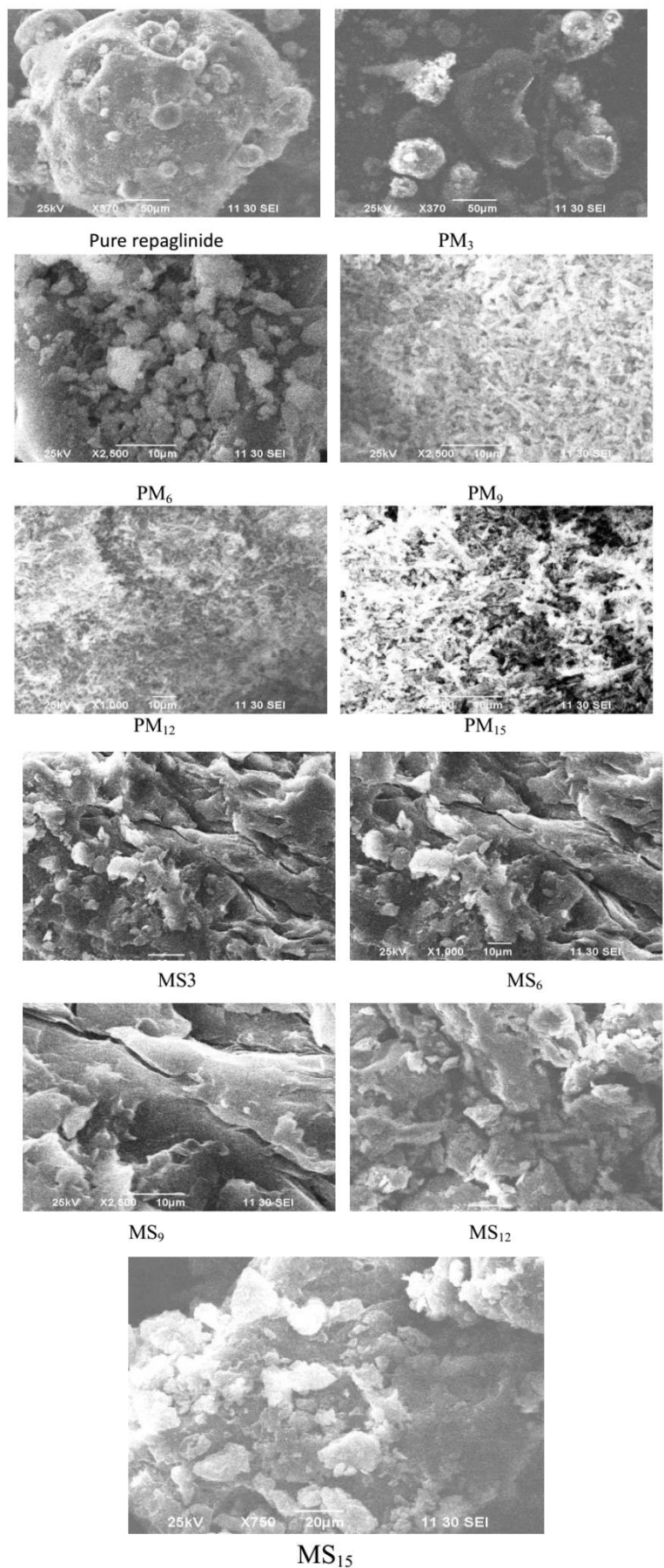
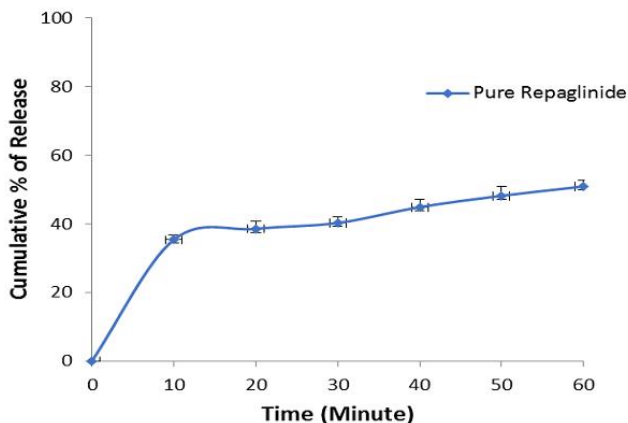
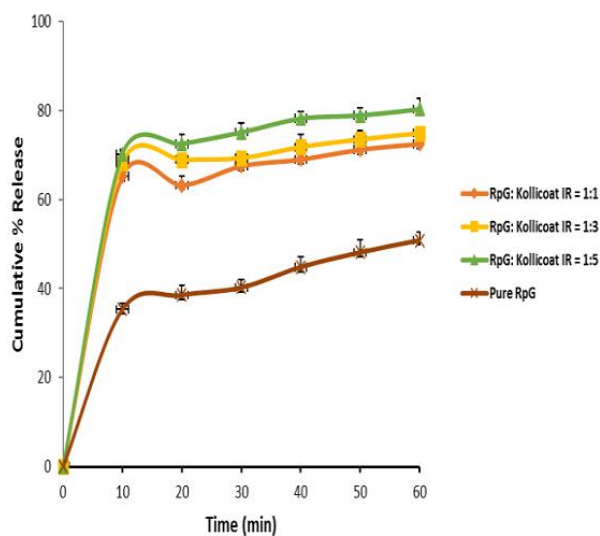


Fig-3: Scanning Electron Microscopy (SEM) of the formulations

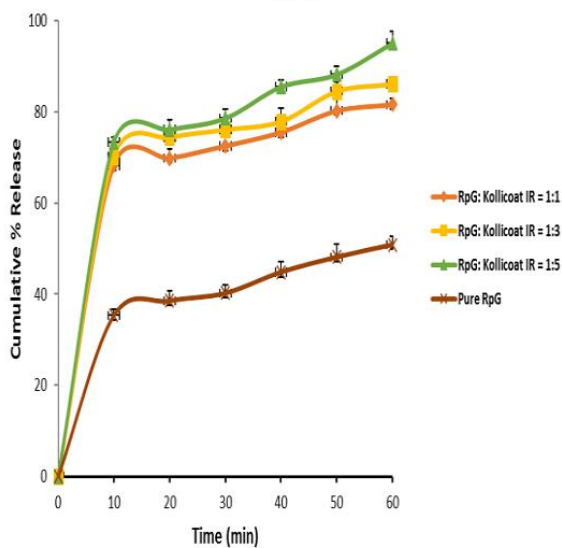
Repaglinide Cumulative % Release



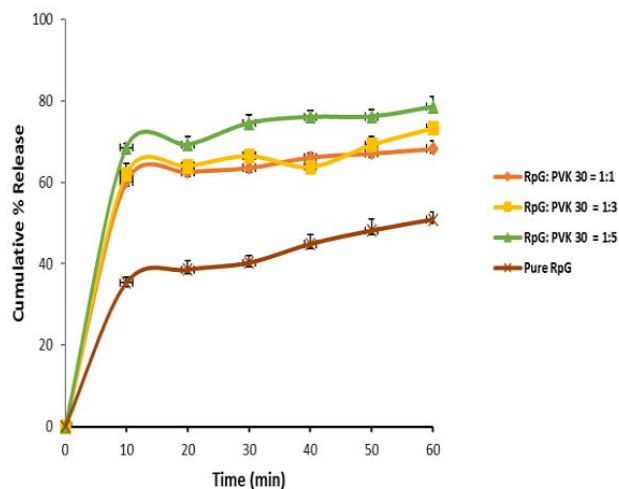
Repaglinide: Kollicoat IR at different ratios by physical mixing



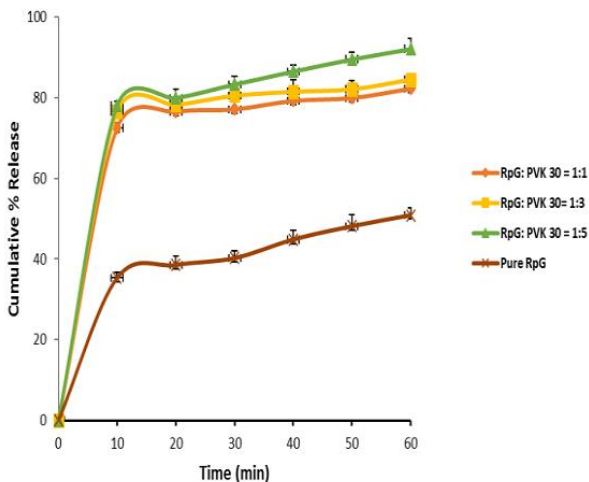
Repaglinide: Kollicoat IR at different ratios prepared by Melt Solvent Method



Repaglinide: PVK 30 at different ratios by physical mixing



Repaglinide: PVK 30 at different ratios prepared by Melt Solvent Method



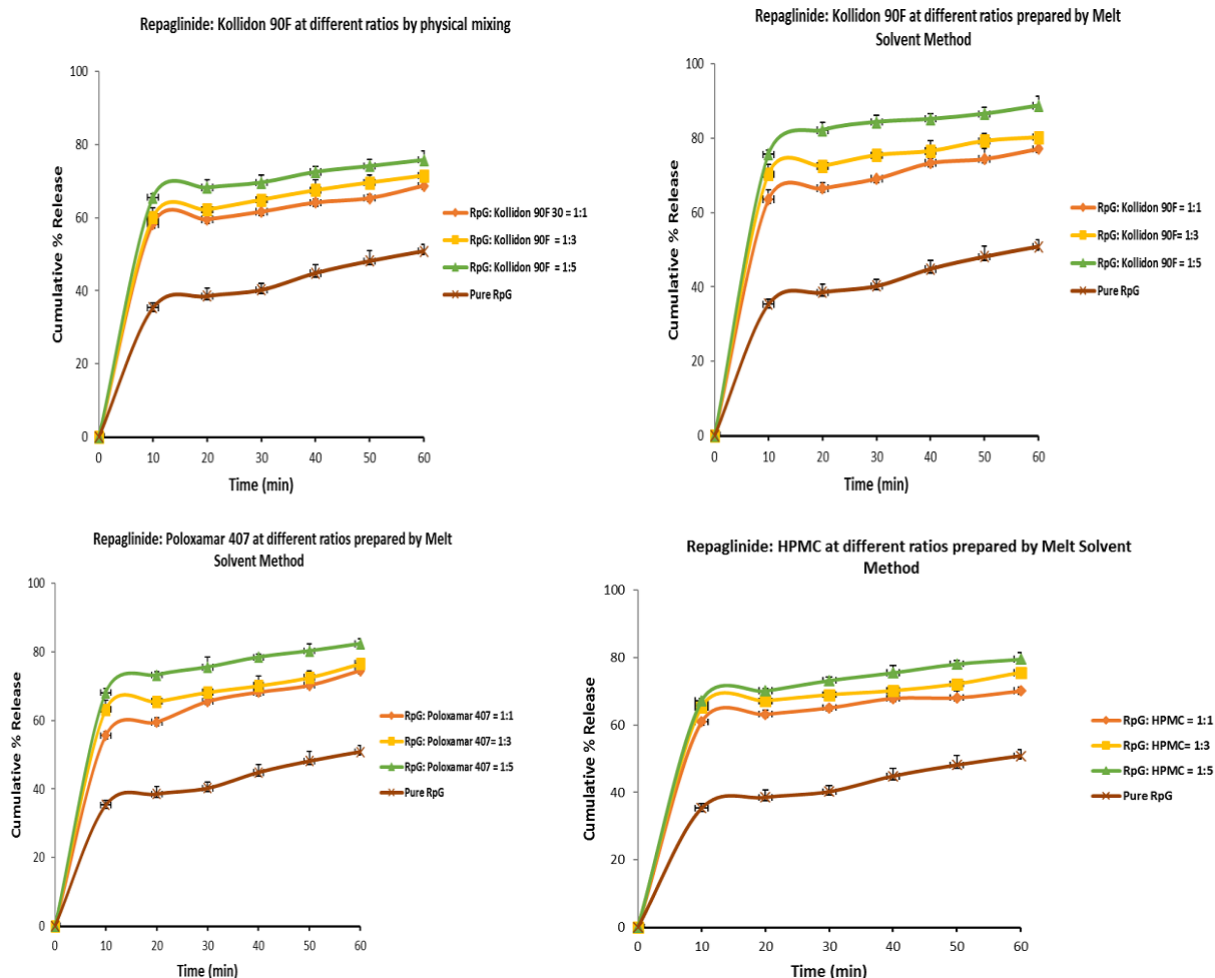


Fig-4: *In vitro* release studies

***In vitro* release studies**

In vitro dissolution studies were carried out three times of each of the formulations (formulations PM₁, PM₂, PM₃, PM₄, PM₅, PM₆, PM₇, PM₈, PM₉, PM₁₀, PM₁₁, PM₁₂, PM₁₃, PM₁₄, PM₁₅, MS₁, MS₂, MS₃, MS₄, MS₅, MS₆, MS₇, MS₈, MS₉, MS₁₀, MS₁₁, MS₁₂, MS₁₃, MS₁₄ & MS₁₅). The cumulative released of repaglinide in dissolution media was 50.8% after 60 minutes which is shown in figure 4. The mean cumulative percent of repaglinide released from PM₁, PM₂, PM₃, PM₄, PM₅, PM₆, PM₇, PM₈, PM₉, PM₁₀, PM₁₁, PM₁₂, PM₁₃, PM₁₄ and PM₁₅ formulations prepared by physical mixing, at different time intervals is shown in Fig. 4. It was observed that the rate of release for PM₃, PM₆, PM₉, PM₁₂ and PM₁₅ was higher than 1:1 and 1:3 formulations. As 75%, 80% and 78% repaglinide was found to be released in case PM₁₂, PM₃ and PM₆ (1:5 ratio) after 60 minutes of dissolution. The increase in dissolution rate of drug due to presence of carriers' polymers which enhanced effective solubilization process and conversion of unstructured/amorphous phases, the dissolution percentage is very higher. Therefore, the improve aqueous solubility and dissolution rate of repaglinide increased significantly in the presence of Kollicoat IR, Kollidon 90F, PVK 30,

HPMC and Poloxamar 407. On the other hand, the formulations MS₃, MS₆, MS₉, MS₁₂ and MS₁₅, produced by Melt Solvent technique showed maximum release after 60 minutes which were nearly 95 % for Kollicoat IR (MS₃), 92 % for PVP K30 (MS₆) and 88% for Kollidon 90F (MS₁₂), 82% for Poloxamar 407 (MS₁₂), 79% for HPMC (MS₁₅), respectively which were much higher than MS₁, MS₂, MS₄, MS₅, MS₇, MS₈, MS₁₀, MS₁₁, MS₁₃, MS₁₄ and all other physical mixing formulations shown in Figure-4. Various studies have also reported that Kollicoat IR, Kollidon 90F, Poloxamar 407, HPMC and PVK30 reduce crystallinity of drugs as well as in amorphous nature of drug in the solid dispersions[21, 22]. Inhibition of Crystallization was attributed to two effects: the interaction between the drug molecule and the hydrophilic polymer due to hydrogen bonding and the entrapment of the drug molecules in the hydrophilic polymeric matrix. In the presence of hydrophilic excipients, drug had better wettability; hence the dissolution of drug was greater in the form of solid dispersion [23, 24]. The order of dissolution enhancement was Kollicoat IR > PVPK30 > Kollidon 90F > Poloxamar 407 > HPMC in solid dispersions as well as in physical mixtures.

CONCLUSIONS

The study has demonstrated that binary and ternary dispersions of repaglinide into water-soluble carrier like Kollicoat IR, PVK 30, Kollidon 90F, Poloxamar 407 and HPMC changed the crystallinity of repaglinide according to the type and amount of the polymer. The formation of repaglinide-Kollicoat IR/PVK 30/ Kollidon 90F solid dispersion destroyed almost completely the crystallinity of the drug and represent a suitable modification for improving its availability. Increase dissolution rate likely increase bioavailability of repaglinide which would be beneficial for better glucose control in diabetic patients. However, further studies are required especially *in vivo* studies to confirm bioavailability.

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