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PREPARATION AND EVALUATION OF SIMVASTATIN ORODISPERSIBLE TABLETS CONTAINING SOY POLYSACCHARIDE AND POTASSIUM POLACRILLIN AS NOVEL SUPERDISINTEGRANTS

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ABSTRACT: Oral bioavailability of Simvastatin is very low (5%) due to bad solubility and effect of first pass. The aim of this work is to enhance its solubility and reformulating it as orodispersible tablet to overcome the two problems. Simvastatin solid dispersions in β- cyclodextrin, hydroxylpropyl-β-cyclodextrin, and hydroxylbutyl-β-cyclodextrin were prepared in different drug: polymer ratios namely 1:1, 1:2, and 1:3 by kneading and solvent evaporation methods. Solid dispersion formation and mixture compatibility was investigated by DSC and FTIR. Based on the results of solubility studies; the best solid dispersion formula was selected and formulated into orodispersible tablet using Emcosoy, K-polacrillin as novel superdisintegrants and mannitol, Pullulan as water soluble diluents and evaluated. The results showed that the increase in drug solubility was dependent on polymer type, concentration and also was affected by preparation method. Simvastatin-hydroxyl-butyl-β-cyclodextrin solid dispersion mixture prepared in 1:2 drug: polymer ratio by solvent evaporation method had a higher solubility. Orodispersible tablet formula prepared by Emcosoy as superdisintegrant, Pullulan as diluent showed least wetting and disintegration times (20 and 35 seconds respectively), faster water absorption rate (82), and the highest dissolution rate where the percentage of drug release reached 100% after 20 minutes.. In conclusion: Orodispersible tablets prepared by Emcosoy as superdisintegrant and pullulan as diluent containing simvastatin-hydroxybutyl-β-cyclodextrin is the best choice to improve its water solubility and hence its bioavailability.

INTRODUCTION: Oral route is the simplest and most important way of drug administration, it offers advantages of convenience of administration and potential manufacturing cost savings [1].

Solid dosage forms have the advantages of small bulk, high stability, accurate dosage, and easy production.

Therefore, many attempts are made to formulate most chemical entities under development as solid dosage forms that also guarantee an effective and reproducible plasma concentration after administration [2]. The main problem associated with oral dosage forms is the difficulty of swallowing mainly for pediatrics, geriatrics, bedridden, and nauseating, or mentally disabled patients [3, 4].

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Fast dissolving tablets are also applicable when local action in the mouth is intended such as a local anesthetic for toothaches, oral ulcers, or cold sores [5]. As a result, the demand for developing new more patient- compliant dosage forms technologies has been increasing [6].

Orally disintegrating systems are dosage forms for oral administration, which when placed in the mouth, rapidly dispersed or dissolved in saliva without the need of water or chewing and can be swallowed in the form of liquid [7, 8]. FDA defines orally disintegrating tablets as "A solid dosage form which contains a medicinal substance or active ingredient which disintegrates rapidly within a matter of seconds when placed upon a tongue" [9].

Recently fast dissolving formulation has been popular as Novel Drug Delivery Systems because they are easy to administer and lead to better patient compliance. In these formulations, after disintegration in the oral cavity, the drug solution can be absorbed partially or completely from the sublingual mucosal blood vessels, or be absorbed from the gastrointestinal tract after swallowed [10-12].

The absorption from the oral cavity and pre-gastric absorption bypasses the first pass metabolism of the liver and the bioavailability of some drugs may be increased [13, 14].

Simvastatin is practically water insoluble crystalline compound and hence poorly absorbed from the gastrointestinal tract. Simvastatin blocks a key step in cholesterol biosynthesis pathway in the liver. It acts by specific and potentially inhibition of 3-hydroxy-3-methyl-glutaryl coenzyme-A (HMG CoA) reductase, which catalyzes the reduction of HMG CoA to mevalonate. It is widely used in the treatment of hypercholesterolemia and dyslipidemia as an adjunct to diet.

Being a BCS Class II drug, the dissolution is a rate-limiting step that controls its oral absorption and high variability in pharmacological effects is expected. Therefore, improvement in the solubility and dissolution rate is essential to enhance its bioavailability [15]. There are various techniques which are commonly used to improve drug dissolution and oral bioavailability, include micronization, solubilization by surfactants, and the formation of solid dispersions.

Solid dispersion depends on melting or dissolution process to disperse one or more active ingredients in a carrier or matrix in the solid state [16]. Increased drug wettability, solubilization by the carrier at the diffusion layer, and the reduction or absence of aggregation of drug particles is the main factors that affect increased drug dissolution [17].

Cyclodextrins (CDs) are cyclic α-1, 4 linked oligosaccharides of α -D-glucopyranose units that have a relatively hydrophobic central cavity and hydrophilic outer surface. [18] The α, β, and γ-CDs consisting of six, seven and eight D-glycosidic bonds into a macro cycle. CDs are classical examples of compounds that form inclusion complexes [19]. The most important structural feature of these compounds is their torous like shape, with a hydrophobic interior cylindrical cavity and hydrophilic faces.

In an aqueous solution, the CD hydrophobic central cavity is capable of forming a stable complex with a guest molecule. Numerous derivatives containing thehydroxyl propyl, methyl, sulfobutyl ether and triethyl substitutents in β -CD are in opposition to be used as new pharmaceutical excipients [20].

The aim of the present investigation is to formulate and optimize simvastatin solid dispersions in β-cyclodextrins, hydroxylpropyl-β-cyclodextrins, and hydroxylbutyl-β-cyclodextrins by different techniques to improve its poor water solubility; the prepared solid dispersion will be formulated into orodispersible tablet, and evaluated.

MATERIALS AND METHODS:

Materials: Simvastatin was kindly supplied by (Saja Pharmaceuticals Co. Ltd., Jeddah, Saudi Arabia); β-cyclodextrins (β-CD), hydroxylpropyl-β-cyclodextrins (H-p-β-CD), and hydroxylbutyl-β-cyclodextrins (H-b-β-CD) were kindly supplied by (Nihon Shukohin Kako Co., Ltd., Japan); Pullulan (DMV International, Veghel, The Netherlands). Emcosoy (RS PHARMA GmbH & Co. KG Rosenberg Germany); Polacrillin Potassium (Libraw Pharma, New Delhi, India). Mannitol (Merck, Darmstadt, Germany); Saccharine Sodium from Caesar and Loretz (Hilden, Germany); Aerosil from Degussa (Frankfurt /M., Germany).other chemicals and reagent were purchased from Sigma-Aldrich (St Louis, MO).

Methodology:

1. **Preparation of Simvastatin Solid Dispersion:** Solid dispersions of simvastatin in β-CD, H-p-β-CD, and H-b-β-CD were prepared by kneading, and solvent evaporation methods as follows:

2. **Solvent evaporation method:** In a glass mortar, drug and polymer were mixed in the selected ratio; methanol was added portion wise with a constant continuous stirring until the mixture completely dissolve. Methanol was evaporated under reduced pressure and the resultant solid dispersions were collected [21].

3. **Kneading method:** In a glass mortar, 50% ethanol solution was added portion wise to the calculated polymer amount according to the selected drug/polymer ratio with trituration until slurry like consistency is obtained. The drug was incorporated into the slurry and trituration was further continued for one hour.

   The prepared slurry was then air dried at 25 for 24 to 48 h and the resulting dried product was pulverized and passed through 80 mesh screen sieve and stored in desiccator over fused calcium chloride [22].

   In this work, simvastatin and polymers were mixed in 1:1, 1:2, and 1:3 drug polymer ratios respectively.

4. **Solubility studies of Simvastatin Solid Dispersion:** Excess samples of plain simvastatin and the prepared drug-solid dispersions were separately shaked for 48 hours in 5ml water at room temperature. Subsequently, the suspensions were centrifuged at 15000 rpm for 30min [23]. 1ml filtrate was diluted properly with methanol. The diluted solutions were spectrophotometrically analyzed for simvastatin concentration at 238 nm.

Evaluation of Solid Dispersion: Based on the results of solubility studies, the solid dispersion mixture showing better solubility was selected and subjected to further evaluation including DSC, FTIR, drug content and *in vitro* release studies.

5. **Differential Scanning calorimetry (DSC) studies:** Samples of plain simvastatin, H-b-β-CD, their physical mixture, and solid dispersion for thermal analysis were weighed (5.00-8.00 ± 0.5 mg) into an aluminum pan, covered with an aluminum lid and crimped into position. The pan was placed in the oven together with a blank (prepared exactly the same way but without the sample). The sample and blank were continuously purged with nitrogen gas and thermograms were recorded over a temperature range of (50-250ºC) with a programmed heating rate of 10°C/min. Temperature calibration was made with an indium standard. The DSC thermograms for the tested samples were recorded and analyzed.

6. **Infrared Spectroscopy (FTIR) studies:** Samples of plain simvastatin, H-b-β-CD, their physical mixture, and solid dispersion were mixed with about 400 mg of dry potassium bromide powder compressed into the transparent disc under pressure of 10.000 to 15.000 psi. The IR spectra were recorded and analyzed.

7. **Drug content:** A pre weighed quantity (10 mg) of the prepared solid dispersion was extracted into methanol and filtered (0.22 mm membrane filter disc - Millipore Corporation). The solid dispersion content was determined by measuring the absorbance at 238nm (using UV/Vis spectrophotometer, Shimadzu 1700) after appropriate dilution with methanol. The drug concentration was determined using standard calibration curve. The mean of three determinations was considered.

8. ***In vitro* Release Studies [24]:** The drug release rate from the prepared solid dispersion was carried out in Erweka-USP dissolution testing apparatus II (paddle method) using 500 ml of phosphate buffer (PH= 6.8) as a dissolution medium at 50 rpm, the temperature was kept constant at 37±0.1°C. Aliquots (5ml) were withdrawn at specific pre-determined time intervals of 5, 10, 15, 30, 45, 60, 70, and 90 minutes with replacement. The absorbance of the drug in each sample was measured spectrophotometrically at 238nm using a Shimadzu UV/Vis double beam spectro-photometer after filtration (0.45 membrane

filter) and the cumulative percentage of drug release was calculated using an equation obtained from a standard curve. The mean of six determinations was considered.

Preparation of Simvastatin Orodispersible Tablet: In this work, Simvastatin orodispersible tablets were prepared using the novel superdisintegrants Emcosoy, and Polacrillin potassium by direct compression. According to formula composition shown in **Table 1**; eight orodispersible formulations of simvastatin were prepared. Preweighed amount of the prepared solid dispersion equivalent to 10 mg simvastatin was mixed with all ingredients in cubic mixer by geometrical dilution for ten minutes. The mixture was directly compressed on a flat 10-mm punch/die set using a manual single punch tableting machine (Erweka Tablet Press-Type EK0) without granulation. A Batch of 50 tablets of each formula was prepared.

TABLE 1: FORMULA COMPOSITION OF SIMVASTATIN ORODISPERSIBLE TABLETS

Component (mg)	Formula							
	F1	F2	F3	F4	F5	F6	F7	F8
Simvastatin SD	170	170	170	170	170	170	170	170
Emcosoy	0	15	30	45	0	15	30	45
Polacrillin Potassium	45	30	15	0	45	30	15	0
Pullulan	75	75	75	75	0	0	0	0
Mannitol	0	0	0	0	75	75	75	75
Aerosil	3	3	3	3	3	3	3	3
Saccharin Sodium	3	3	3	3	3	3	3	3
Magnesium stearate	3	3	3	3	3	3	3	3
Talc	1	1	1	1	1	1	1	1
Total (mg)	300	300	300	300	300	300	300	300

SD: Solid dispersion

Evaluation of the prepared simvastatin orodispersible tablets:

1. **Weight variation:** Twenty tablets were randomly selected from each formulation and separately weighed (Shimadzu digital balance BL-220H) and their average weight and standard deviation were calculated

2. **Thickness:** Ten tablets from each formulation were randomly taken and their diameter and thickness were measured at two different positions with a micrometer screw gauge. The average value was then calculated.

3. **Drug content:** For the content uniformity test, ten tablets were weighed and pulverized to a fine powder, a quantity of powder equivalent to single dosage unit was extracted with methanol and simvastatin content was determined as previously mentioned in calculating drug content in the prepared solid dispersion.

4. **Hardness:** The average breaking strength (Kg/cm^2) of ten tablets of each formula was determined by hardness tester.

5. **Friability:** Ten tablets of each formula were accurately weighed and placed in the drum of friabilator rotated at 25 rpm for a period of 4 minutes, then dusted, and reweighed. The percentage weight loss was calculated and taken as a measure of friability.

6. ***In vitro* dispersion time:** Ten tablets were separately placed in a 25 ml beaker containing 10 ml of distilled water (PH= 6.8) at 37±0.5ºC and the time required for complete dispersion was determined.

7. **Wetting time and water absorption ratio** [25, 26]**:** Five circular tissue papers of 10 cm diameter are placed in a petridish with a 10 cm diameter. 10 ml of water-containing amaranth a water soluble dye is added to petridish. A tablet is carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of the tablet is noted as a wetting time. Tablets were separately weighed (W_a) and carefully placed onto the surface of a piece of tissue paper twice folded in a 5 cm diameter petri dish containing 6 ml of aqueous amaranth solution.

The time (in seconds) for complete wetting (water reaches the upper surface of the tablet) was noted and recorded as the wetting time. The wetted tablet was carefully removed and reweighed (W_b).

Water absorption ratio (R) through the tablet was then determined according to the following equation: $R= 100 \times (W_a - W_b)/ W_b$

8. ***In vitro* Release Studies:** The drug release rate from the prepared orodispersible tablets was carried out in Erweka-USP dissolution testing apparatus II (paddle method) following the same conditions applied to determine the drug release rate from the prepared solid dispersion. Aliquots (5ml) were withdrawn at specific pre-determined time intervals of 2.5, 5, 7.5, 10, 12.5, 15, 20, 25, and 30 minutes with replacement. The cumulative percentage of drug release was calculated using the equation obtained from a standard calibration curve. The mean of six determinations was considered. For comparison T 50% and T 90% were calculated and compared.

RESULTS AND DISCUSSION:

Solubility studies: Effect of solid dispersion, polymer type, preparation method, and drug polymer ratio on the drug water solubility was studied and the results (**Table 2**) showed that the drug solubility was increased in all prepared solid dispersion mixtures, and the increment of drug solubility was proportional to the polymer concentration. A hydroxyl butyl derivative of cyclodextrin showed better solubility results than hydroxyl propyl derivative than cyclodextrin and solvent evaporation method was superior than kneading method.

Hydroxy-butyl-*β*-CD has surfactant-like properties owing to the hydrophilicity of its exterior surface which can lower the interfacial tension between poorly soluble drugs and the dissolution medium, resulting in a higher dissolution rate [27].

β-CD with longer C-2 substituted group increases the hydrophilic character of the molecule and hence stronger surfactant action on drug/water contact angle is expected and higher dissolution rates are obtained. This could explain the better solubility results of hydroxy-butylated *β*-CD than hydroxy propylated form [28].

Based on these results, Simvastatin-Hydroxy-butyl-β-cyclodextrin solid dispersion mixture prepared in 1:2 drug: polymer ratio respectively by solvent evaporation method was selected and subjected to further evaluation including DSC, FTIR, drug content, and in vitro release studies.

Despite formula F9b that prepared in 1:3 drug polymer ratio showed higher solubility results it was not selected for further study because the tablet weight in orodispersible formulation is critical factor and restricted to a certain degree that not affect patient compliance.

TABLE 2: CHARACTERIZATION OF THE PREPARED SOLID DISPERSIONS

Polymer	D: P*	Code	S_{Kn}	D.C** %	Code	S_{Ev}	D.C** %
β-CD	1:1	F1a	2.254	97.2	F1b	4.523	98.5
β-CD	1:2	F2a	4.686	96.4	F2b	6.312	97.1
β-CD	1:3	F3a	5.714	97.2	F3b	7.324	98.1
H-p-β-CD	1:1	F4a	4.333	98.1	F4b	6.314	98.1
H-p-β-CD	1:2	F5a	5.954	98.2	F5b	8.943	98.2
H-p-β-CD	1:3	F6a	6.826	97.6	F6b	9.645	97.1
H-b-β-CD	1:1	F7a	6.113	96.6	F7b	9.876	98.2
H-b-β-CD	1:2	F8a	9.223	98.2	F8b	12.324	97.6
H-b-β-CD	1:3	F9a	10.114	97.3	F9b	13.107	99.4

S_{Kn}: Solubility (µg/ml) Kneading method. S_{Ev} : Solubility (µg/ml) Solvent evaporation method. *: Molar Drug/polymer Ratio. **: Drug Content.

Differential Scanning Calorimetry (DSC) studies: Figure 1 shows the DSC thermograms of simvastatin, H-b-β-CD, their physical mixture, and the prepared solid dispersion. Simvastatin shows a sharp endothermic melting peak at 138°C. This peak was retained in the thermogram of the physical mixture with no appearance of new peaks that excludes any incompatibility.

In solid dispersion thermogram; the peak completely disappeared indicating formation of solid dispersion and conversion of drug from crystalline to amorphous state. The disappearance of the drug melting peak also indicates that it penetrated into H-b-β-CD cavity replacing the water molecule [29].

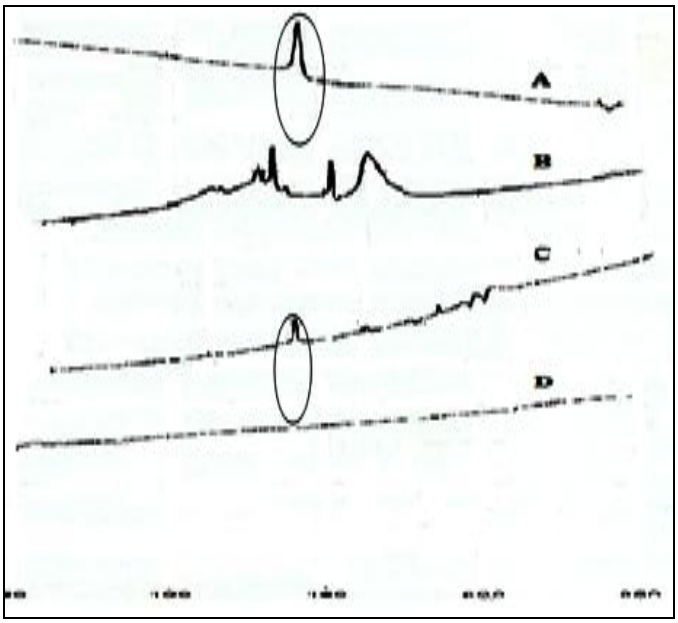

FIGURE 1: DSC THERMOGRAMS OF (A) SIMVASTATIN, (B) H-b-β-CD, (C) PHYSICAL MIXTURE, (D) SOLID DISPERSION

Infrared Spectroscopy (FTIR) studies: FTIR spectrum of simvastatin showed the main characteristic peaks at 3553 cm-1 (free O–H stretching vibrations); 3011, 2959, and 2872 cm-1 (C–H stretching vibrations); and 1714 cm-1 (stretching vibration of ester and lactone carbonyl functional groups). They were all retained in physical mixtures and SD, which clearly indicate that no chemical interaction exists between pure drug and polymer in SD, **Figure 2**.

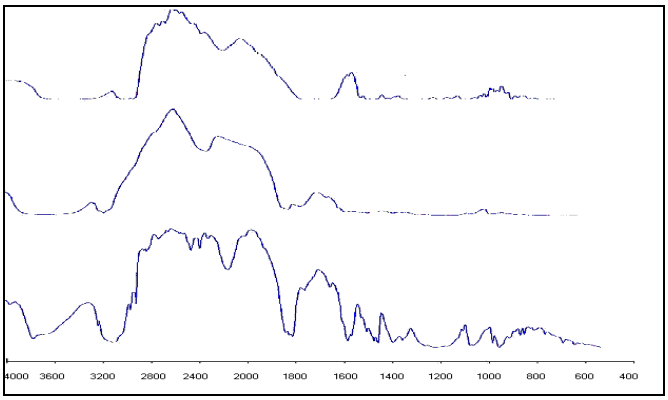

FIGURE 2: FTIR SPECTRA OF (A) SIMVASTATIN, (B) H-b-β-CD/SMVASTATIN PHYSICAL MIXTURE, (C) H-b-β-CD/SMVASTATIN SOLID DISPERSION

Drug content: Results of drug content (Table 2) showed excellent loading capacity of the drug into the polymer matrix in the prepared solid dispersion independent on the polymer type and preparation method. The percentage drug content ranged from 96.4% to 99.4.

Figure 3 shows the effect of cyclodextrin complexation on the release profiles of simvastatin from the prepared solid dispersion in different ratios. Results indicate that the release rate of simvastatin was significantly increased when dispersed in different cyclodextrin derivatives. Hydroxyl butyl derivative of cyclodextrin showed better solubility results than hydroxyl propyl derivative than cyclodextrin and the higher the polymer concentration in the prepared solid dispersion the faster and higher release rate occurred.

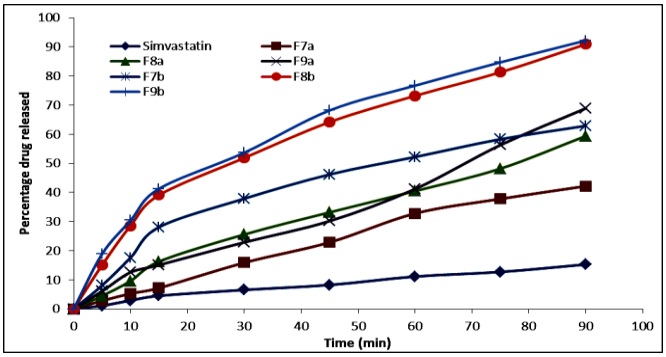

FIGURE 3: DISSOLUTION PROFILES OF THE PREPARED SIMVASTATIN SOLID DISPERSIONS

Preparation of Simvastatin Orodispersible Tablet: Simvastatin orodispersible tablets were prepared using the novel superdisintegrants Emcosoy and Polacrillin potassium either alone or in combinations by direct compression. Emcosoy is natural soy polysaccharides, that have no starch or any sugar and contains 75% dietary fiber. It is an ideal choice for low calorie and diabetic applications. In tablet manufacture; it had evidenced a fast and efficient disintegration power over an extended range of hardness values with improved dissolution characteristics [30]. Polacrillin Potassium is a derivative of cross-linked polymer of polycarboxylic acids. In contact with aqueous media; it shows a very high swelling power leading to a very fast disintegration without the formation of lumps. It imparts excellent strength to the tablet and has anti-adherent characteristics that prevent sticking to the dyes and punch [31, 32].

Water insoluble diluents such as microcrystalline cellulose and dicalcium phosphate were excluded from the preparation of orodispersible formulae due to the expected objectionable feeling of grittiness in the mouth [33]. Soluble diluents, mannitol and Pullutan were selected as diluent. Pullulan, a linear glucosic polysaccharide with high water solubility is an edible, bland and tasteless polymer; it is commercially used in the manufacture of breath freshener or oral hygiene products. Pullulan is almost completely inert, excluding interaction with products it intended to deliver [34].

Evaluation of the prepared Simvastatin Orodispersible Tablets: Table 3 shows the results of post-compression tablet physical evaluation; all the prepared tablets are characterized by a uniform thickness, diameter and weight indicating efficient mixing. The formulated tablets exhibited low weight variation that varies between 295 to 311mg; the drug content was between 98.32 – 101.37% with low standard deviation values, the thickness of tablets varies from 2.2 to 2.4 mm. All formulations showed good mechanical resistance and breaking strength, where the friability values were all less than 1% and varied between 0.213 - 0.465%, the hardness values were in the range of 3.78 - 2.41 Kg/cm^2 that lies within the acceptable pharmacopoeial limits as per USP XXVII.

TABLE 3: POST-COMPRESSION PHYSICAL EVALUATION OF SIMVASTATIN ORODISPERSIBLE TABLETS

Formula	Drug content	Weight variation	Tablet thickness	Hardness	Friability
F1	99.23 ±1.24	297±0.11	2.3 ±0.01	3.78 ±0.13	0.213
F2	101.37 ±1.43	311±0.24	2.2 ±0.02	3.43 ±0.21	0.298
F3	99.42 ±1.75	298±0.08	2.3 ±0.01	3.02 ±0.11	0.272
F4	99.32 ±1.88	295±0.13	2.4 ±0.01	3.17 ±0.24	0.303
F5	98.13 ±1.39	305±0.25	2.2 ±0.01	2.86 ±0.17	0.376
F6	99.02 ±1.48	308±0.18	2.3 ±0.03	2.61 ±0.25	0.422
F7	98.34 ±1.39	298±0.21	2.4 ±0.02	2.53 ±0.14	0.465
F8	101.05 ±1.52	297±0.12	2.3 ±0.01	2.41 ±0.25	0.413

The behavior of the prepared simvastatin orodispersible tablets in contact with water was studied by measuring wetting time, water absorption rate, in vitro dispersion time, and drug release rate from the tablets. Results are summarized in **Table 4**.

All proposed simvastatin orodispersible formulae were acceptable and their behavior in contact with water is very good as indicated by the short wetting time that ranged between 20±2 to 56±3 seconds, a rapid water absorption rate that ranged between 82±3 to 46±2, and short disintegration time that ranged between 35±4 to 77±2 seconds.

TABLE 4: CHARACTERIZATION OF HYDROPHILIC PROPERTIES OF SIMVASTATIN ORODISPERSIBLE TABLETS

Formula	Wetting time (sec.)	Water absorption ratio	*In vitro* dispersion time (sec.)	(%) Drug release in 5 minutes	T 50% (min.)	T 90% (min.)
F1	40 ±4	70±5	68 ±2	30.2 ±3.21	11.23	27.34
F2	35 ±3	65±3	50 ±2	25.3 ±2.12	13.76	24.54
F3	24 ±3	76±2	41 ±3	54.7 ±3.53	4.27	11.34
F4	20 ±2	82±3	35 ±4	60.5 ±2.32	3.75	9.75
F5	56 ±3	46±2	77 ±2	31.3 ±4.13	11.56	29.24
F6	50 ±4	51±3	75 ±2	33.4 ±4.23	10.54	20.65
F7	42 ±4	57±1	64 ±3	38.3 ±2.93	8.23	18.43
F8	37 ±3	62±2	56 ±2	48.9 ±4.23	5.57	13.35

Wetting time is an indicator of the hydrophilicity of the inner structure of the tablet and used excipients. Thus wetting time of a dosage form is related to the contact angle. The lower the wetting time the quicker is the tablet disintegration [35]. The disintegration time of orodispersible tablets is generally less than 1 minute and actual disintegration time that patient can experience ranges from 5 – 30 seconds [36]. To study the effect of different formulation factors on the behavior of the prepared simvastatin orodispersible tablets in contact with water, the results of these tests will be discussed in details. The diluent effect was studied by comparing the results of F1 to F4 and F5 to F8. Results showed that pullulan is more efficient than mannitol, where F1 and F4 showed superior results

as indicated by shorter wetting and disintegration times as well as faster water absorption rate. The superdisintegrant effect was studied by comparing results of F1 to F4 and F5 to F8. Emcosoy showed higher wetting properties and disintegration power than polacrillin-K, where F4 and F8 showed shorter wetting and disintegration time and faster water absorption rate than F1 and F5 respectively.

The effect of combination of both superdisintegrants polacrillin-K and Emcosoy on the tablet behavior in contact with water was studied by comparing the results of F3 to F4, F7 to F8, F1 to F2 and F5 to F6. The results showed that mixing of Emcosoy improved the hydrophillic characteristics of polacrillin-K containing orodispersible formulae where F2 and F6 showed better results than F1 and F5 respectively, and this effect was proportional to Emcosoy ratio in the superdisintegrant mixture.

The dissolution profile of different prepared simvastatin orodispersible tablet formulae (Figure 4) indicated a higher, faster, and maximum drug release from formula F4 and F3 followed by F8 and F7, where the percentage of drug release reached 100%, 99.1%, 96.2% and 95.8% respectively after 20 minutes. These results are compatible with that of the wetting and disintegration time results and this insures the effect of different formulation factors on the tablet hydrophilicity.

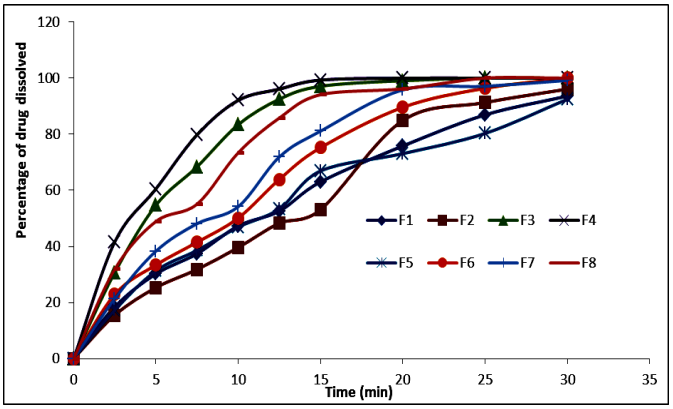

FIGURE 4: DISSOLUTION PROFILES OF THE PREPARED SIMVASTATIN ORODISPERSIBLE TABLETS

Further analysis of dissolution data indicated that formulae F4, F3, and F8 showed initial rapid drug release that reached 60.5%, 54.7%, and 48.9% respectively after 5 minutes, this can be attributed to higher hydrophilic properties and stronger swelling power of Emcosoy in these formulations, while presence of the very hydrophilic pullulan as diluent in formulae F4 and F3 resulted in a higher initial drug release and the release rate was also dependent on the pullulan ratio in both formulations. Formula F8 that depends on mannitol as diluent showed least initial drug release due to its lower hydrophilicity than pullulan.

For comparison; T50 and T90 for the release rate were calculated and compared (Table 4). The prepared simvastatin orodispersible tablet formulae F4, F3 and F8 reached their dissolution half-lives after 3.75, 4.27, and 5.57 minutes while 90% of drug content was released after 9.75, 11.34, and 13.35 minutes respectively.

CONCLUSION: Depending on the results of the study it can be concluded that; H-b-β-CD is an efficient polymer to prepare simvastatin solid dispersion and the preparation method together with the drug polymer ratio were critical and significantly affects the drug solubility.

The selection of the suitable superdisintegrants for the preparation of fast dissolving tablets is highly effective, where Emcosoy significantly affected all tablet behavior in contact with water. Also Pullulan is a promising effective diluent to be used in preparation of orodispersible tablet formulations containing hydrophobic drugs.

Declarations of interest: The authors report no any conflict of interest

REFERENCES:

1. Ahmad Zaheer, Maurya Naveen, Mishra K. Santosh, Khan Imran. Solubility enhcement of poorly water soluble drugs: A review. International Journal of Pharmacy &Technology 2011:3(1): 807-23
2. Lima AAN, Sobrinho JLS, Correa JR RAC, Rolim Neto PJ. Alternative Technologies to Improve Solubility of Poorly Water Soluble Drugs. Lat. Am. J. Pharm. 2008; 27(5):789-97.
3. [3] Kaushik D, Dureja H, Saini TR. Mouth dissolving tablets: A review. Indian Drugs-Bombay 2004:41:187-93.
4. [4] Chue P, Welch R, Binder C. Acceptability and disintegration rates of orally disintegrating risperidone tablets in patients with schizophrenia or schizoaffective disorders. Can J Psychiatry 2004:49:701-3.
5. Chang RK, Guo X, Burnside BA, Couch RA. Fast dissolving tablets. Pharm Technol, 2000:24:52-58.
6. Bhushan SY, Sambhaji SP, Anant RP, Mahadik KR. New drug delivery system for elderly. Indian Drugs, 2003:37:312-18.

7. Venkateswara SS, Nyshadham JR, Joseph AF. Recent technological advances in oral drug delivery - a review. Pharm. Sci. Tech. Today, 2000:3:138-45.
8. Porter SC. Novel drug delivery: Review of recent trends with oral solid dosage forms. Am. Pharm. Rev. 2001:85:28-35.
9. Bandari S, Mittapalli RK, Gannu Rao YM. Orodispersible tablet: An overview. Asian J. Pharm. 2008:2:2-11.
10. Berner B, Birudaraj R, Shen S, Li X.Buccal permeation of buspirone: mechanistic studies on transport pathways. J. Pharm. Sci. 2005:94:70-78.
11. Ishikawa T, Koizumi N, Mukai B. Pharmacokinetics of acetaminophen from rapidly disintegrating compressed tablet prepared using microcrystalline cellulose (PH-M-06) and spherical sugar granules. Chem Pharm Bull. 2001:49: 230-32.
12. Price TM, Blauer KL, Hansen M Stanczyk F. Single-dose pharmacokinetics of sublingual versus oral administration of micronized 17 beta-estradiol. Obstet Gynecol. 1997:89:340-45.
13. Gohel M, Patel M, Amin A, Agarwal R, Dave R, Bariya N. Formulation design and optimization of mouth dissolving tablets of nimesulide using vacuum drying technique. AAPS Pharm Sci Tech. 2004:5(3):10–15.
14. Panigrahi D, Baghel S, Mishra B. Mouth dissolving tablet: An overview of preparation techniques, evaluation and patented technologies. Journal of pharmaceutical research. 2005:4(3): 33-38.
15. Prasad Tandale, Dipti Joshi, Gaud RS. Formulation and Evaluation of Extended Release Solid Dispersions containing Simvastatin. Asian Journal of Biomedical and Pharmaceutical Sciences, 2011:1(3):13-19.
16. Ansari MT, Sunderland VB. Solid dispersions of dihydroartemisinin in polyvinylpyrrolidone. Arch. Pharm. Res. 2008:31(3):390-98.
17. Rashmi Dahima, Ashish Pachori, Sanjay Netam. Formulation and evaluation of mouth dissolving tablets containing amlodipine besylate solid dispersion. Int.J. ChemTech Res. 2010:2(1):706-15.
18. Fernandes CM, Teresa VM, Veiga FJ. Physicochemical characterization and in vitro dissolution behavior of nicardipine–cyclodextrins inclusion compounds. Eur J Pharm Sci. 2002:15:79–88.
19. Guosong Chen, Ming Jiang. Cyclodextrin-based inclusion complexation bridging supramolecular chemistry and macromolecular self-assembly. Chem. Soc. Rev. 2011:40:2254-66.
20. Manolikar MK, Sawant MR. Study of solubility of isoproturon by its complexation with b-cyclodextrin. Chemosphere. 2003:51:811–16.
21. Patel RP, Patel MM. Physico-chemical characterization and in vitro dissolution bahaviour of Simvastatin β–cyclodextrin inclusion compounds. Drug Delivery Technology, 2007:7(5):50-56.
22. Veiga F, Teixeira-Dias JC, Kedzierewicz F, Sousa A, Maincent P. Inclusion complexation of tolbutamide with - cyclodextrin and hydroxypropyl--cyclodextrin. Int. J. pharm. 1996:129:63-71.
23. Camelia Nicolescu, Corina Aram A, Angela Nedelcu, Crina- Maria Monciu. Phase solubility studies of the inclusion complexes of repaglinide with β-cyclodextrin and β-cyclodextrin derivatives. FARMACIA, 2010:58(5):620-28.
24. Patil JS, Kattimani VK, Shiralashetti SS, Marapur SC, Kamalapur MV. Utilization of Superdisintegrants in the Design, Evaluation and Optimization of Orodispersible Tablets containing Simvastatin-Cyclodextrin Inclusion Complexes. RJPS 2011:1(3):209-15.
25. Chaudhari PD, Chaudhari SP, Kohle SR, Dave KV, More DM. Formulation and evaluation of fast dissolving tablets of famotidine. Indian Drug. 2005:42:641-9.
26. Battue SK, Repay MA, Maunder S, Rio MY. Formulation and evaluation of rapidly disintegrating tablet Fenoverine tablets: Effect of superdisintegrants. Drug. Dev. Ind. Pharm. 2007:33:1225-32.
27. Bhanja SB, Ellaiah P, Martha SK, Sahu A, Padhy SK. Preparation and Evaluation of Solid Dispersions of Poorly Soluble Drug Repaglinide. Asian Journal of Biochemical and Pharmaceutical Research. 2011:3(1):201-21.
28. Yan Baia, Gui Ying Xua, Hong Yuan Sunb, Ai You Haob, Hong Zhi Maob et. Al. Effect of Substituted Group of β-Cyclodextrin Derivatives on the Dispersing of Carbon Nanotubes. Journal of Dispersion Science and Technology 2010:31(3):353-58.
29. Raun P, Yang B, Guang MF, Dan Z. Improving the solubility of amelopsin by solid dispersions and inclusion complexes. Journal of Pharmaceutical and Biomedical analysis 2005:38:457-64.
30. Hardik Patel, Viral Shah and Umesh Upadhyay. New pharmaceutical excipients in solid dosage forms – A review. Int. J. of Pharm. & Life Sci. 2011:2(8):1006-19.
31. Rowe RC, Sheskey PJ, Owen SC. Handbook of Pharmaceutical Excipients. 5th Ed. Pharmaceutical Press 2006:532-34.
32. Bele MH, Derle DV. Effect of polacrilin potassium as disintegrant on bioavailability of diclofenac potassium in tablets: a technical note. AAPS PharmSciTech. 2012:13(3):756-9.
33. Vineet Bhardwaj, Mayank Bansal, Sharma PK. Formulation and Evaluation of Fast Dissolving Tablets of Amlodipine Besylate Using Different Super Disintegrants and Camphor as Sublimating Agent. American-Eurasian Journal of Scientific Research 2010:5(4):264-69.
34. Cheng KC, Demirci A, Catchmark JM. Pullulan: biosynthesis, production, and applications. Applied Microbiology and Biotechnology 2011:92(1):29-44.
35. Radke RS, Jadhav JK, Chajeed MR. Formulation and evaluation of orodispersible tablets of baclofen. Int J Chem Tech Res. 2009:1:517-21.
36. Paramita Dey, Sabyasachi Maiti. Orodispersible tablets: A new trend in drug delivery. Journal of Natural Science, Biology and Medicine2010:1(1):2-5.

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