Original Research Article

Design and investigation of metformin hydrochloride–Indion-254 complex for dispersible tablets

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Abstract

Objective: Metformin is a first-line agent for the treatment of Type 2 diabetes. The taste of metformin hydrochloride drug powder is bitter and its formulation are orally used. The objective of this study was to make a complex of metformin hydrochloride with Indion-254 resin for the purpose of preparation of dispersible tablet.

Materials and Methods: This study formulated metformin hydrochloride–Indion-254 complexes with different proportion of resin with fixed amount of drug as well as mixed at varying speed which improved the flowability.

Results: The resulted complex was investigated by the help of Fourier Transform- Infrared Spectroscopy, differential scanning calorimetry, and X-ray diffraction which were used to confirm complexation and to differentiate its features from the individual ingredients and the physical mixtures of ingredients.

Conclusion: The formulated metformin hydrochloride–Indion-254 complex showed better drug loading as well as good release in mixed phosphate buffer in 200 ml.

Keywords: Complex, drug dissolution, Indion-254, metformin hydrochloride, taste masking

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INTRODUCTION

In formulation development, resin polymers, which are anionic or cationic, are used independently for a particular function or combined with pharmaceutical ingredients such as dextromethorphan, streptomycin, and metformin for an intended purpose as taste masking.[1-8] Metformin has a bitter taste and is mainly used for Type 2 diabetes but is also indicated for polycystic ovarian syndrome.[9-11] In this study, a brand of sodium polystyrene sulfonate (Indion-254), a strong acid cationic resin, was used with metformin hydrochloride to produce a taste-masked dispersible complex, which will ultimately be used to prepare a formulation suitable for patients who have difficulty in swallowing a solid dosage form.[12]

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MATERIALS AND METHODS

Metformin hydrochloride received as gift sample from Intas Pharmaceuticals, India, and other chemicals and solvents used were of analytical grades purchased from different suppliers of India.

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Preparation of metformin hydrochloride–Indion-254 complex

Specified amount of resin as per Table 1 was weighed and added to the 60 ml distilled water in beaker. The beaker was placed on the water bath and it was stirred on magnetic stirrer for 1½ h at 50°C. After this period of stirring, weighed amount of metformin hydrochloride was dissolved in mixture and stirred on magnetic stirrer for 24 h. After 24 h, mixture was filtered under vacuum and rinsed with distilled water. The obtained residue was dried at 50°C and it was analyzed for percentage drug loading using equation below:

$$\% \text{ drug loading on resin} = ([C_i - C_f]/C_i) \times 100 \quad \text{Eq 1}$$

Where C_i = Initial concentration of metformin hydrochloride in seventy milliliters of mixture and C_f = Final concentration of filtrate.

Characterization of resin complex

Drug–resin physical mixture and the drug–resin complex of metformin hydrochloride and sodium polystyrene sulfonate (Indion-254) were characterized using Fourier transform-infrared spectroscopy (PerkinElmer precisely spectrum 400 spectrometer and the universal attenuated total reflectance sampling accessory), differential scanning calorimetry (DSC) (Setsys Evolution TG-TMA calorimeter), and X-ray diffraction methods.

Drug–resin complex evaluation

The metformin hydrochloride–Indion-254 complex was analyzed for particle size (SEM and microscope methods), flow properties, and drug release in different medium and volumes in dissolution apparatus-2 at 75 RPM.

RESULTS

Characterization of metformin hydrochloride–Indion-254 complex

In Figure 1a, wavenumbers were at 3135.48, 1547.75, 1045.35, and 634.37/cm for metformin hydrochloride; in Figure 1b, wavenumbers were at 3437.65, 1641.03, 1181.28, 1031.86, 830.27, and 674.42/cm for Indion®-254; and in Figure 1c, metformin hydrochloride and Indion physical mixture looks similar to the Indion graph but with sharper peaks as seen in Metformin. Wavenumbers were at 1179.60, 3415.70, 1028.67, and 674.94/cm and compared to the physical mixture graph Figure 1d, metformin hydrochloride and Indion resin complex, the complex graph demonstrated some peaks around the 1500 and between 3400 and 3300 wavenumber/cm. The wavenumbers include 3346.47, 1555.07, 1172.72, 1012.43, and 674.09/cm.

Table 1: Composition of various metformin hydrochloride-Indion®-254 complexes

Metformin HCl (g)	Indion®-254 (g)	Percentage drug loading (mean±SD) (%)
1	3	75.49±0.109
1	4	77.29±0.484
1	5	81.53±1.322
1	6	84.40±1.573
1	5 (change in speed of stirrer)	77.50±2.220
1	6 (change in speed of stirrer)	80.49±0.538

HCl: Hydrochloride, SD: Standard deviation

In Figure 2a, the two peaks were at 237.89°C and 338.33°C with an onset at 234.17°C and 299.10°C, respectively; in Figure 2b, one peak was seen at 103.42°C; in Figure 2c, two peaks observed at 235.15°C and 100°C; and in Figure 2d, one peak noticed at 95.78°C was observed. All the above differential scanning calorimetry graphs demonstrated endothermic heat flow.

In Figure 3a, the graph for metformin hydrochloride demonstrated sharp peaks along the X-axis (abscissa) from 10 to 50[2]. Peaks were observed at approximate values of 12.5°, 13°, 14.5°, 22°, 25°, 27°, 27.5°, 28°, 33°, 34.75°, 35.8°, 36.3°, 37.5°, and 39.9° with minor peaks thereafter until 50°. The major peaks were at 22.75°, 18°, 29.75°, 23.5°, 31.5°, and 28.5°, respectively, in order of intensity/counts. In Figure 3b, the graph showed no significant sharp peaks as was seen for metformin hydrochloride; in Figure 3c, graph for the drug–resin complex appears similar to that of Indion-254 with no significant sharp peaks; and in Figure 3d, graph is similar to Indion-254; however, there were a number of sharp peaks noticed at various points including those at approximately 12.5°, 18°, 22.75°, 23.5°, 27°, 28°, 29°, 30°, 33°, 35°, 36°, 36.25° and 45°.

Analysis of metformin hydrochloride

The melting point for metformin hydrochloride began at 234.4ºC ± 4.34°C and ended at 253.8°C ± 4.71°C. The thermal values obtained using the capillary tube and the DSC methods exhibited similar melting onset readings of 234.4 ± 4.34 for the former and 234.17 for the latter.

Drug–resin complex evaluation

The flow property of metformin HCl and its complex with Indion resin in different proportion (1:4, 1:6) was determined by the fixed funnel method and angle of repose was calculated. The observation was recorded in Table 2.

The metformin–Indion-254 complexes demonstrated better flow properties than metformin alone, and the complex 1:6 showed better flowability than metformin hydrochloride and the complex of ratio 1:4.

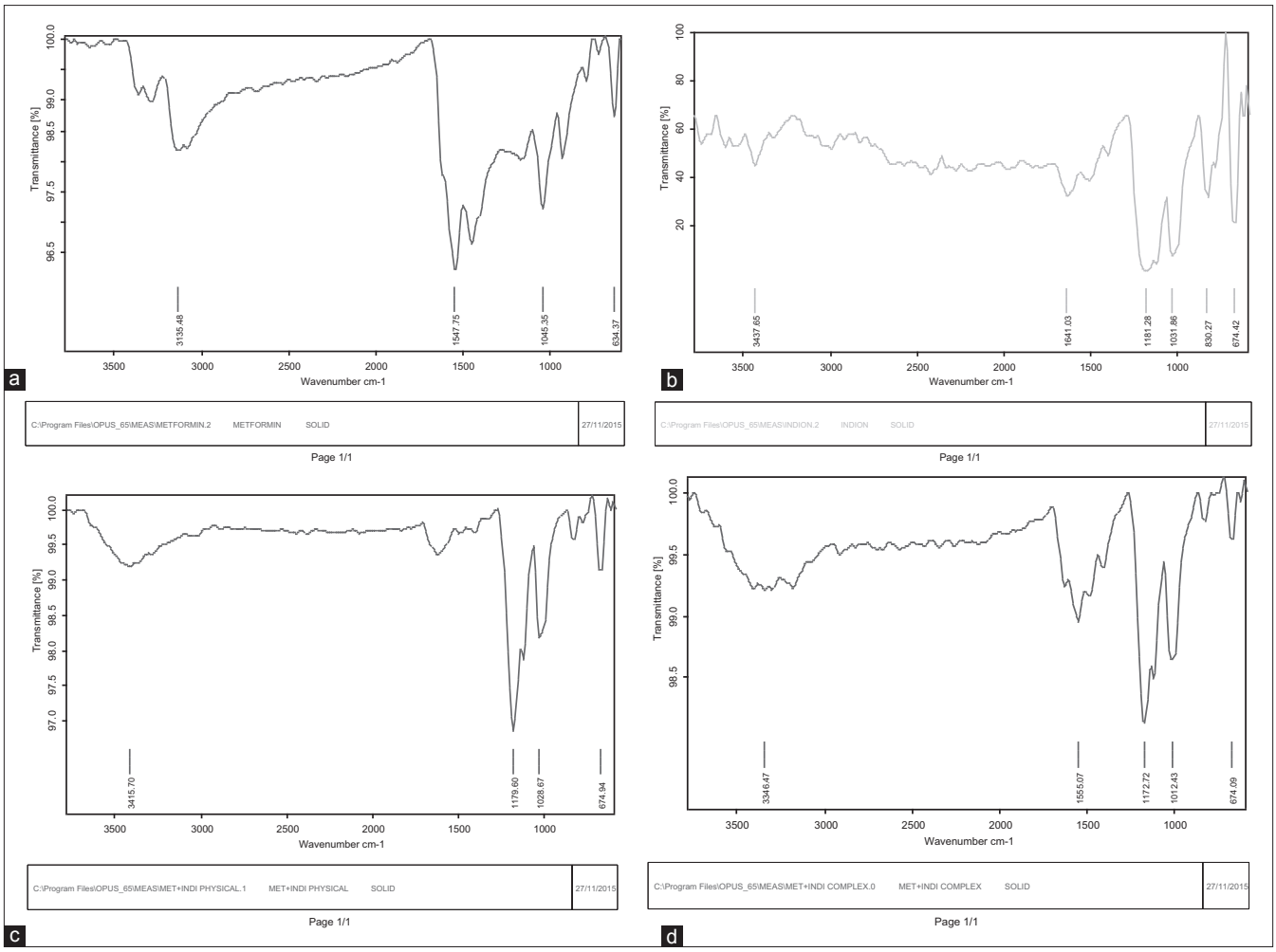

Figure 1: Fourier transform-infrared spectroscopy of metformin hydrochloride and its complex with resin. (a) Fourier transform-infrared spectroscopy of metformin hydrochloride, (b) Fourier transform-infrared spectroscopy of Indion-254 resin, (c) Fourier transform-infrared spectroscopy of physical mixture of metformin hydrochloride and Indion-254 resin, (d) Fourier transform-infrared spectroscopy of the metformin hydrochloride-Indion®-254 resin complex

Table 2: Flow properties of metformin hydrochloride and complexes

Item description	Angle of repose (°)	Flow property
Metformin HCl	35.80±4.22	Good/poor
Metformin HCl-Indion®-254 (1:4)	28.07±3.66	Excellent/very poor
Metformin HCl-Indion®-254 (1:6)	27.09±1.60	Excellent/passable

HCL: Hydrochloride

Drug release studies of in different medium and volumes

The drug release of metformin HCl was determined in distilled water and phosphate buffer pH 6.8, and data were recorded in Table 3.

Figure 4a shows % cumulative drug release in distilled water (4 ml) using magnetic stirrer, Figure 4b shows % cumulative drug release in phosphate buffer pH 6.8 (4 ml) using magnetic stirrer. Figure 4a and 4b shows that the drug release is slightly greater for DRC 1:4 than DRC 1:6 and also observed was more drug release in phosphate buffer pH 6.8 than in distilled water.

Figure 4c represents % cumulative drug release in phosphate buffer pH 6.8 (200 ml) in dissolution apparatus and Figure 4d represents % cumulative drug release in simulated gastric fluid pH 1.2 (200 ml) in dissolution apparatus. In Figure 4c and 4d, DRC 1:4 released more metformin in phosphate buffer pH 6.8 than in simulated gastric fluid pH 1.2.

It was observed that the metformin HCl–Indion 1:4 complex demonstrated higher dissolution efficiency in water and phosphate buffer pH 6.8 than the 1:6 ratio complex. In addition, higher results were seen for complex 1:4 in 200 ml of phosphate buffer pH 6.8 compared to comparable volume of simulated gastric fluid pH 1.2.

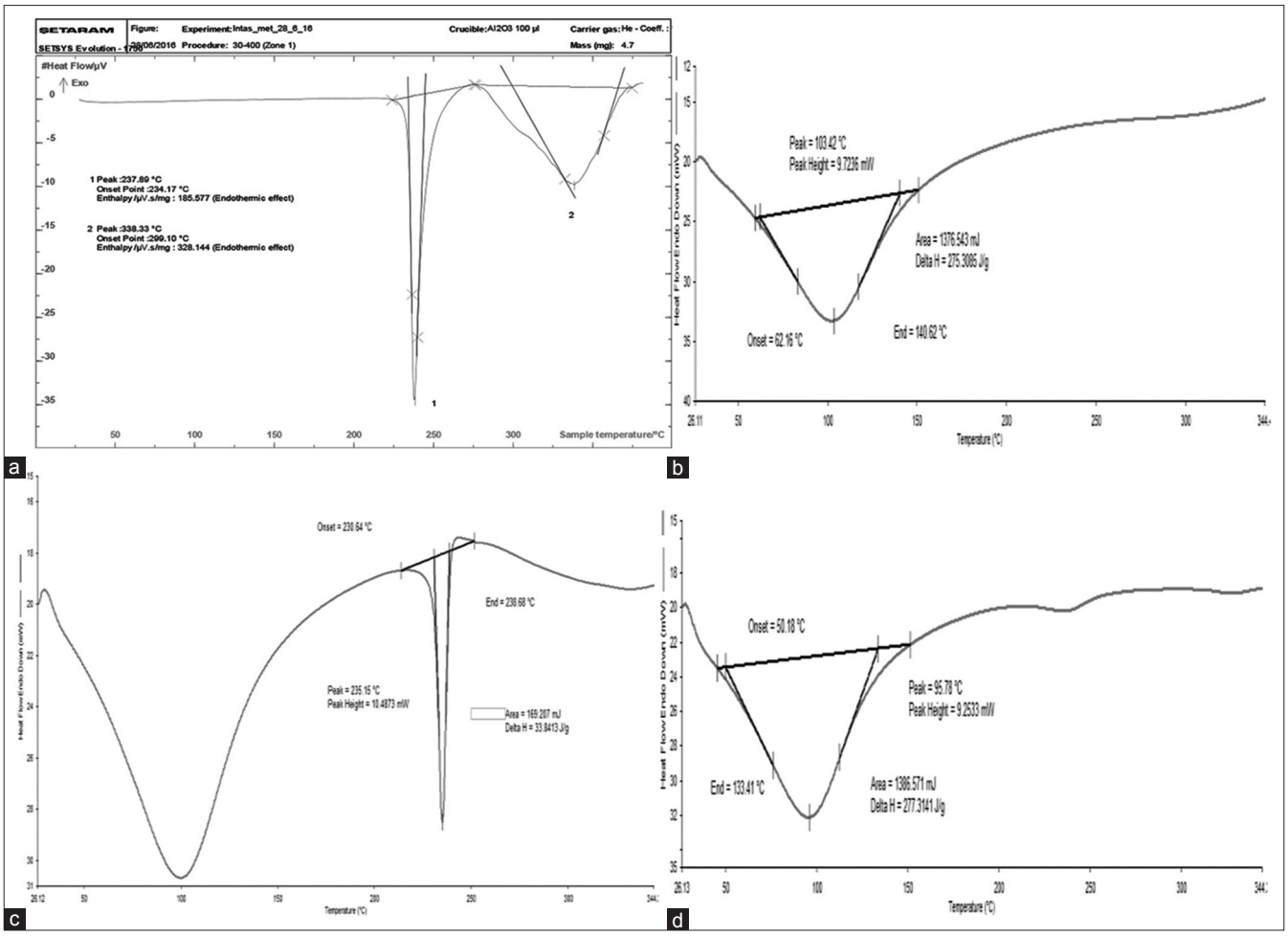

Figure 2: Differential scanning calorimetry of metformin hydrochloride and its complex with resin differential scanning calorimetry (a) metformin hydrochloride, (b) differential scanning calorimetry Indion-254 resin, (c) physical mixture of metformin hydrochloride and Indion-254 resin, (d) metformin hydrochloride–Indion-254 resin complex

Table 3: Drug release of metformin hydrochloride in different media and conditions

Description	Media	Volume (ml)	AUC	MDT	DE	Maximum percentage drug release compared to pure drug
Metformin HCl-Indion®-254 (1:4)	Distilled water	4	5152.316	315.8416 s	0.028624	2.016
Metformin HCl-Indion®-254 (1:6)	Distilled water	4	4950.753	329.7915 s	0.027504	1.350
Metformin HCl-Indion®-254 (1:4)	Phosphate buffer pH 6.8	4	44576.95	100.7495 s	0.495299	36.990
Metformin HCl-Indion®-254 (1:6)	Phosphate buffer pH 6.8	4	44165.94	101.2397 s	0.490733	32.474
Metformin HCl-Indion®-254 (1:4)	Simulated gastric fluid pH 1.2	200	3095.009	13.97117 min	0.128959	18.082
Metformin HCl-Indion®-254 (1:4)	Phosphate buffer pH 6.8	200	16514.84	13.15134 min	0.917491	101.642

HCL: Hydrochloride, AUC: Area under the curve, MDT: Mean dissolution time, DE: Dissolution efficiency

DISCUSSION

Changes in external factors were found to influence the drug-loading percentage of ion exchange resins and hence can be used to optimize this process. In this study, an increase in the speed of the magnetic stirrer increased the loading percentage of the 1:5 and 1:6 ratios. Other factors that can affect drug-loading percentage include stirring time, temperature, particle size, pH of the media, and type of method used. The unbounded drug in the filtrate is measured using ultraviolet-infrared spectroscopy or high-pressure liquid chromatography, and then, this value is subtracted from the initial concentration to determine the amount of drug that was bound to the resin.[13-15]

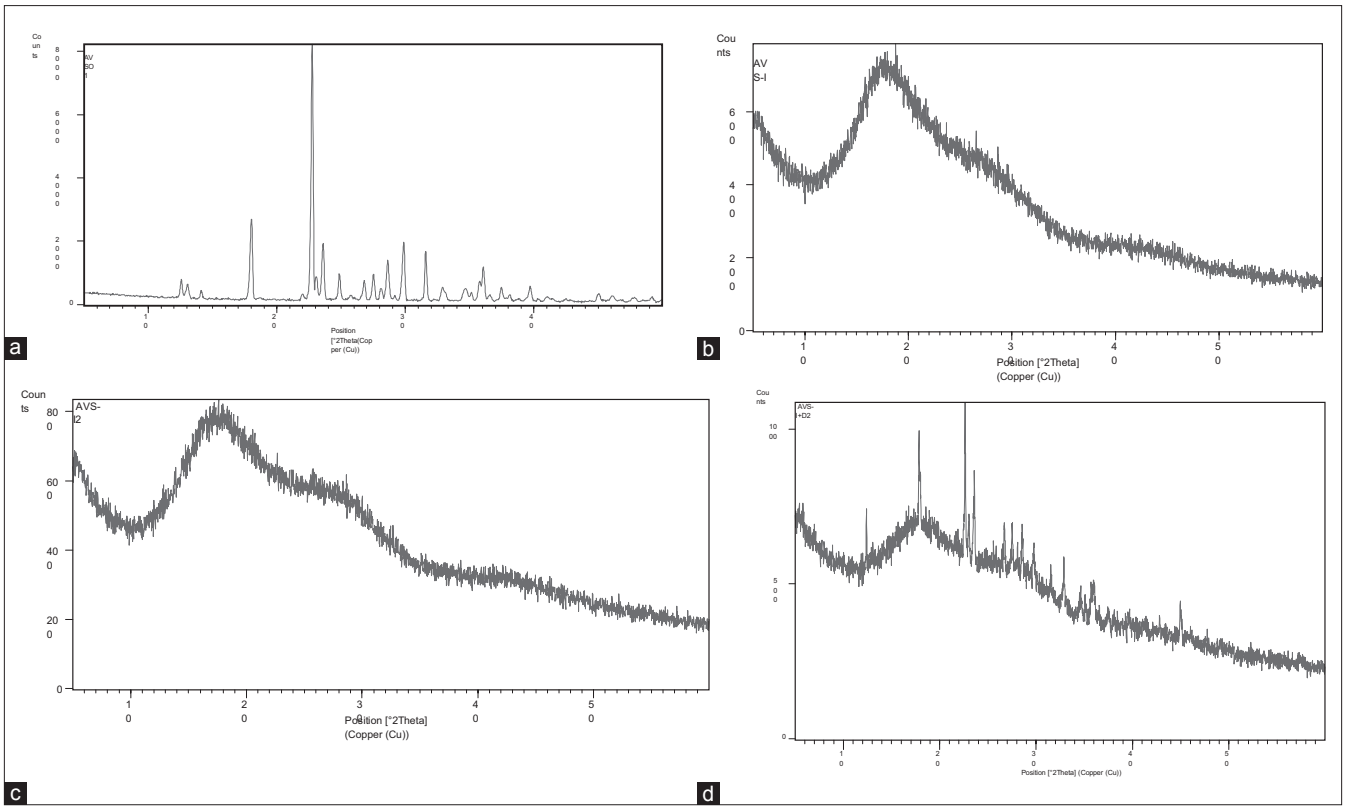

Figure 3: X-ray powder diffraction of metformin hydrochloride and its complex with resin. X-ray powder diffraction (a) metformin hydrochloride, (b) Indion-254, (c) metformin hydrochloride–Indion-254 resin complex, (d) physical mixture of metformin hydrochloride and Indion-254 resin

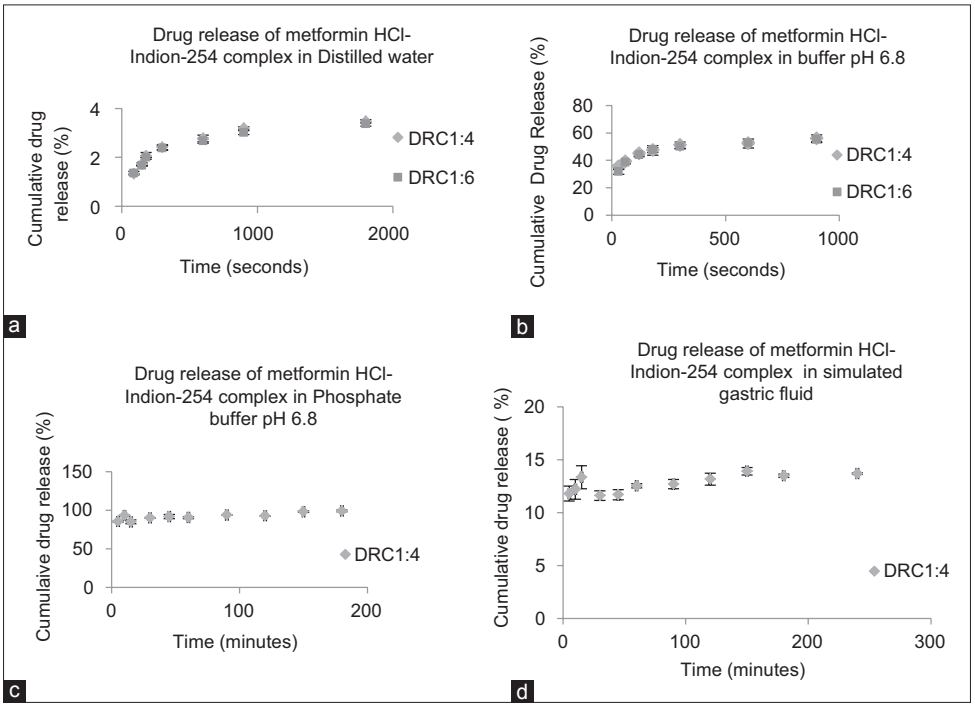

Figure 4: Percentage cumulative drug release in different media and condition. Drug release study (a) of metformin HCl–Indion®-254 complex in distilled water, (b) metformin HCl–Indion-254 complex in buffer pH 6.8, (c) metformin HCl–Indion-254 complex in phosphate buffer pH 6.8, (d) metformin HCl–Indion-254 complex in simulated gastric fluid

When the complex is formed, it is physically and chemically different to a physical mixture of the individual components. These differences were observed in the graphs demonstrated for infrared spectroscopy, X-ray

diffraction, and differential scanning calorimetry. In the X-ray diffractogram, the physical mixture maintained some peaks that were seen also in the metformin hydrochloride graph; this indicated their crystalline structure. However, this was not observed for the resin or drug–resin complex graphs, confirming the presence of complexation through suitable bonding. In the complexed form, the bitter group, such as the amine group in metformin, binds to the resin and hence masks the bitter taste of the drug.[16] Therefore, the physical mixture will not be as effective as the complex in taste masking because the physical mixture behaves as two independent substances as were seen in the calorimetry results where two distinct melting points were observed for the physical mixture as compared to one for the complex. For this study, taste-masking properties were tested by the dissolution/drug release method, which determines the concentration of the drug released in various media compared to the pure drug. According to the guidelines of the Federation International Pharmaceutique and American Association of Pharmaceutical Scientists, <10% of a drug released/dissolved in 5 min constitutes effective taste masking; nevertheless, this also depends on the bitterness extent/index/threshold of the respective drug. Therefore, if the bitterness threshold for metformin hydrochloride can be acquired, in terms of concentration, then this will verify whether the approximate 37% release of metformin hydrochloride observed for 4 ml of phosphate buffer pH 6.8 would provide any taste-masking effect.[17-20] Other probable methods consist of the electronic tongue or alternative automotive device that measures the bitter level of a drug in comparison to standard, *in vivo,* and *ex vivo* procedures.[21] The taste-masking results for this study showed the complex to be more stable in water, a neutral medium, than in phosphate buffer pH 6.8, as less of the drug was released/dissociated from the resinate/complex opposed to pure drug in similar medium and volume, hence minimizing the bitter taste of metformin hydrochloride. Consequently, metformin hydrochloride is cationic and binds to the anionic resin to form the metformin HCl-Indion-254 complex; hence, the ions present in the media according to pH dissociate the drug from the complex.

More resin added increases the amount of binding sites available for the drug to bond, therefore higher the drug loading percentage. However, higher resin ratios are not suitable to formulate into a tablet as the resulting product will require to be too large in size. In our study, DRC 1:4 released more metformin in 4 ml of water and phosphate buffer pH 6.8 than DRC 1:6 as a result of the bonding extent at a higher loading percentage. In similar respect to its bonding, metformin hydrochloride was released more in phosphate buffer pH 6.8 than in simulated gastric fluid pH 1.2, which may explain why metformin is not released or is less absorbed in the stomach as compared to the small intestines.[22] Furthermore, the results of the study demonstrated that with a larger volume of medium, the more metformin is released out of the complex as was observed with phosphate buffer pH 6.8 in 4 ml compared to 200 ml. It, therefore, is imperative to analyze the complex based on the formulation to be developed as an oral disintegrating product will require to be tested in a volume of usually 10 ml or less as oppose to a solid dosage form which will require a volume of 200 ml or more.

Particle size of the drug or resin was stated earlier to affect the drug-loading percentage of the complex; however, particle size can also influence the taste properties such as mouthfeel as well as the flow and manufacturing process. Finer particles have a greater surface area hence a faster dissolution but decreased flowability.[23-26] Direct compression is the pharmaceutical process favored by most industries compared to other methods such as wet granulation and requires good flow properties of the formulation blend which includes excipients. Hence, the excipients selected are to enhance this and other attributes of the formulation.[27]

CONCLUSION

The formulated metformin hydrochloride-Indion-254 complex showed capabilities to provide taste-masking and disintegrating properties and hence can be developed into an oral- or water-disintegrating tablet.

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Conflicts of interest

There are no conflicts of interest.

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