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Development and evaluation of oral fast disintegrating film of ranitidine HCl by solvent casting method

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Abstract: Here, we developed oral fast disintegrating film (ODF) of ranitidine hydrochloride (RHCl) by solvent casting method and assessed the impact of various formulation ingredients i.e. polymer concentration, type of plasticizers and superdisintegrants. Optimized film was developed with hydroxypropyl methyl cellulose (HPMC E5, 3% w/v) as film matrix, propylene glycol (PG) (10% w/w of polymer) as plasticizer and Pearlitol flash® (PF) (10% w/w of polymer) as release modifier. This film was chosen based on appearance, transparency, thickness, folding endurance and *in vitro* disintegration time (DT). Later on, optimized film was loaded with drug (50% w/w of polymer) (A12), which disintegrated within 15 seconds and released 81% of RHCl within two minutes. Furthermore, FTIR studies confirmed the absence of drug film ingredients interaction. SEM showed even distribution of RHCl and all excipients. Thus, A12 will be palatable for geriatric patients and helpful to avoid premature intestinal degradation.

Keywords: HPMC E5, films, ranitidine HCl, disintegration, Pearlitol flash®

INTRODUCTION

In recent years, various dosage forms have been employed to improve the bioavailability (Mehmood *et al.*, 2020, Preis *et al.*, 2013) and avoid the hepatic metabolism of the drug (Bharti *et al.*, 2019). These include salt formation, solid dispersion, micro/nanoparticles, microbeads, oral fast dissolving tablets, orodispersible films, etc. Among them oral fast dissolving/disintegrating films (ODF) have emerged as an important carrier to overcome these issues (Tokuyama *et al.*, 2009). The importance of the ODF lies in its rapid disintegration in oral cavity without need of water for swallowing (Song *et al.*, 2019), owing to its large surface area (Dixit and Puthli, 2009). They also enhances permeability, bioavailability and fastens the onset of action of drug compared to the conventional oral dosage forms (Cilurzo *et al.*, 2018). It is a highly preferred carrier for the drugs encountering first pass effect (Irfan *et al.*, 2016). Moreover, ODF improves compliance of geriatric, pediatric (Ouda *et al.*, 2020), bedridden, nauseous, and mentally ill patients with dysphagia (Lopez *et al.*, 2015).

ODFs are fabricated with plasticized blends of hydrophilic polymers (Zayed *et al.*, 2020) using various techniques that include solvent/slurry casting method, hot melt extrusion method, semi-solid casting, solid dispersion extrusion, rolling and printing (Dixit and Puthli, 2009, Hoffmann *et al.*, 2011, Irfan *et al.*, 2016). Other than solvent casting method, all other methods need expensive equipment and expertise. Therefore, the solvent casting method was preferred for the fabrication of ODF. In this method, selection of polymer, plasticizer and superdisintegrating agent are imperative for development of optimum film formulation (Senta-Loys *et al.*, 2017).

In literature, ODF of various drugs were developed using hydrophilic polymers. These includes polyvinyl pyrrolidone K30 (Verma *et al.*, 2018), carboxymethyl cellulose (Boateng *et al.*, 2013), sodium alginate (Boateng *et al.*, 2013), lycoat NG73 (El-Setouhy and Abd El-Malak, 2010), hydroxyethyl cellulose (El-Setouhy and Abd El-Malak, 2010), hydroxypropyl methyl cellulose (Brniak *et al.*, 2015, El-Setouhy and Abd El-Malak, 2010, Mushtaque *et al.*, 2020, Singh *et al.*, 2018, Takeuchi *et al.*, 2020), polyvinyl alcohol (Mashru *et al.*, 2005), chitosan (Singh *et al.*, 2018), lycoat RS720 (Manda *et al.*, 2018), albizia and khaya gum (Bonsu *et al.*, 2016). While frequently used plasticizers are polyethylene glycol (Bala and Sharma, 2018, Jermain *et al.*, 2018), glycerin (Manda *et al.*, 2018, Singh *et al.*, 2018), glycerol (Boateng *et al.*, 2013) and propylene glycol (Satyanarayana and Keshavarao, 2012). Superdisintegrating agents used are cross carmellose sodium (Verma *et al.*, 2018), mannitol (Manda *et al.*, 2018, Singh *et al.*, 2018), sodium starch glycolate (Zhang *et al.*, 2018) and cross povidone (Zhang *et al.*, 2018).

In this study, RHCl was incorporated in ODF and so far only loaded in fast disintegrating tablets (Rishikesh *et al.*, 2013). RHCl is H_2 receptor antagonist and used in the treatment of peptic, duodenal and gastric ulcers, gastroesophageal reflex disease, erosive esophagitis and Zollinger-Ellison syndrome (Verma *et al.*, 2018). However, due to its short half-life (2.2h), poor absorption from gastro intestinal tract (GIT) owing to microbial degradation (Basit and Lacey, 2001) and hepatic

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metabolism, which ultimately lead to low bioavailability i.e. 50% (Wei and Zhao, 2008). So, ODF seems a suitable carrier for RHCl as oral mucosa is highly vascularized, enables quick entry into blood, avoids the hepatic metabolism of RHCl and thus facilitates the maximum absorption from oral cavity (Hua, 2019).

This research work investigated the development of ODF of RHCl by choosing HPMC E5 as matrix polymer owing to its biocompatibility, ease of handling and excellent film forming capabilities. Furthermore, also tested the effect of various plasticizer and superdisintegrating agent. To the best of our knowledge, it was not attempted before. Finally, optimized film was evaluated by solid state characterization and *in vitro* release study.

MATERIALS AND METHODS

Materials

Ranitidine HCl (RHCl) (Batch No RH 856 11 17) was obtained as a gift sample from Axis Pharmaceuticals Sahianwala road Faisalabad (Pakistan). Sodium starch glycolate (SSG, Glycolys) and Pearlitol Flash® (PF) (Mannitol Starch) were received as gift samples from Roquette Frères (France). Hydroxypropyl methyl cellulose (HPMC E5) was obtained from Alfa Aesra (Germany). Kyron T-314 (KT-314) was obtained as a gift sample form Corel Pharma Chem (India). Polyethylene glycol (PEG 400), propylene glycol (PG), and cross carmellose sodium (CSS) were obtained from Daejung and metals Co., Ltd. (Korea). Glycerin (GLY) was obtained from Sigma-Aldrich (Germany). All other excipients and chemicals were of analytical grade.

Solvent casting method

ODF was prepared by solvent casting method with minor modifications to previously reported method (Alayoubi *et al.*, 2017). In brief, aqueous solution-I was prepared by dissolving HPMC E5 (1-6% w/v) and superdisintegrating agents (5, 7.5 and 10% w/w of polymer) in distilled water under constant stirring and later kept for one hour to remove air bubbles. Aqueous solution-II was prepared by dissolving various plasticizers (10% w/w of polymer) in distilled water with continuous stirring for 15 minutes. Afterwards, aqueous solution I and II were mixed and stirred for 30 minutes. The resultant solution was sonicated to remove air bubbles, casted in petri dish and dried overnight at room temperature. The resultant blank film was carefully removed from petri dish, cut into 3×2 cm stamp shaped films, wrapped in aluminum foil and stored in desiccator until further use. Drug loaded film was prepared in similar way, where specific proportion of RHCl (50% w/w of polymer) was added in aqueous solution-I.

Screening for optimized blank film

For suitable plasticizer and HPMC E 5 concentration

Different plasticizers (PEG 400, PG and GLY) at constant concentration (10% w/w of polymer) were tested with different concentration of HPMC E5 (1-6% w/w). The obtained films were evaluated for thickness, folding endurance and DT to select optimized blank film (Preis *et al.*, 2013).

For selection of superdisintegrating agent

This trial was designed to select the best super-disintegrating agents among CCS, SSG, KT-314 and PF and its optimum concentration. Based on the screening studies, the optimized drug loaded film was selected for further characterization.

Characterization of optimized drug loaded film

Thickness

Thickness was measured at five different points of each film by using digital micrometer and mean value was reported (Kumar *et al.*, 2014).

Folding endurance

Film was repeatedly folded at the same place until it breaks. The number of the times the film is folded without breaking is taken as the folding endurance value and mean was reported (Chandra *et al.*, 2018).

Tensile strength

Tensile strength was measured by using Universal testing machine (INSTRON® 3366-10KN, Instron® GmbH Germany). In brief, film strip (5×2 cm^2) was clipped to clamp, where one side was fixed and other was moveable. To determine the tensile strength film was pulled by the upper clamp at the rate of 5 mm/minute until it breaks (Nair *et al.*, 2013).

In vitro disintegration time (DT)

The 6 cm^2 film strip was placed in petri dish having 10 mL of USP phosphate buffer solution (PBS) (pH 6.8). DT was considered, when film was completely disintegrated after immersion in fluid and mean reported (Chandra *et al.*, 2018).

Drug content

ODF of 6 cm^2 was completely dissolved in 20 mL of PBS (pH 6.8) in beaker. Then solution was filtered through 0.45µm syringe filter. Filtrate was suitably diluted with PBS (pH 6.8) and scanned on UV/Vis Spectrophotometer (CECIL CE7400S) at 315nm. The content of RHCl was determined by using previously developed calibration curve (Brniak *et al.*, 2015).

Solid state characterization

The drug-polymer compatibility was investigated by FTIR analysis in the spectral region of 4000-500cm^{-1}. X-ray diffraction (XRD) was carried out to evaluate the effect of film formulation process on crystallinity of drug. Scanning electron microscope (SEM) was used to examine the surface morphology of drug and ODF.

In vitro drug release

In vitro release of RHCl loaded film was carried out in a beaker containing 200mL PBS having pH 6.8, maintained

at 37±0.5˚C and stirred at 50 rpm (Zaman *et al.*, 2020). 5 mL of sample was withdrawn at specific time intervals (0, 0.25, 0.5, 0.75, 1, 2, 3, 4, 5 and 10 minutes) and substituted by 5mL of fresh prewarmed (at 37˚C) dissolution medium. The samples were passed through 0.45 µm syringe filters and analyzed for drug content by measuring the absorbance at 315 nm.

STATISTICAL ANALYSIS

All experimental data was expressed as mean ± standard deviation (SD) and calculated by OriginPro version 9.5.

RESULTS

Selection of optimized oral film

Selection of plasticizer and HPMC E5 concentration

Different batches of ODF with different concentrations of HPMC E5 and various plasticizers were prepared and evaluated for appearance, thickness, folding endurance, and DT as illustrated in fig. 1a, b, & c.

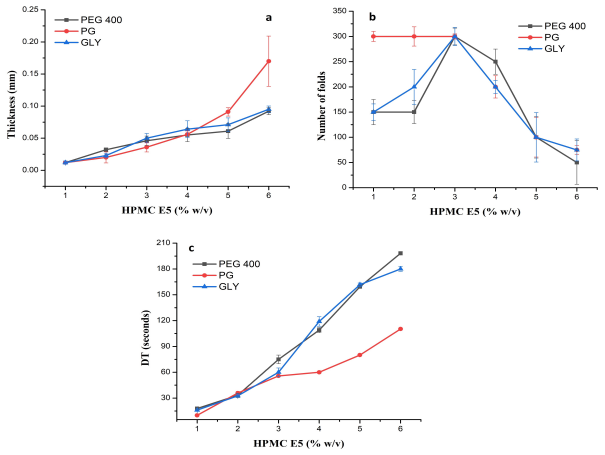

Fig. 1: Effect of HPMC E5 concentration and various plasticizers (PEG 400, PG and GLY) on a: Thickness; b: Folding endurance and c: DT of ODF. Error bars represents ±SD (n=5).

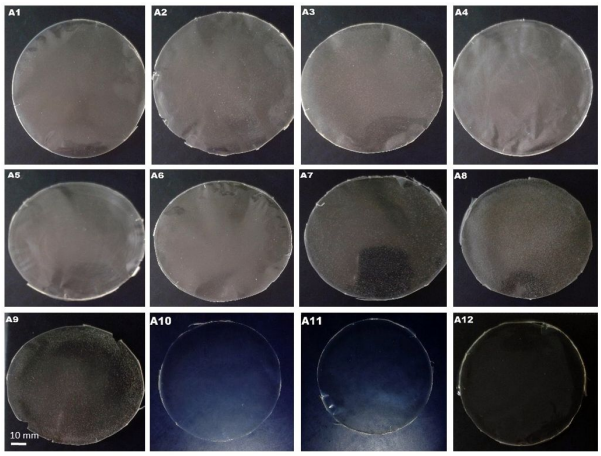

Fig. 2: Optical images of drug loaded films with different superdisintegrating agent.

Optimized formulation

After initial detailed screening studies, A12 ODF containing HPMC-E5 (3%w/w) as film matrix, PG (10% w/w of polymer) as plasticizer and PF (10% w/w of polymer) as superdisintegrating agent was chosen as optimum formulation, loaded with RHCl (50% w/w of polymer) and was used for further analysis.

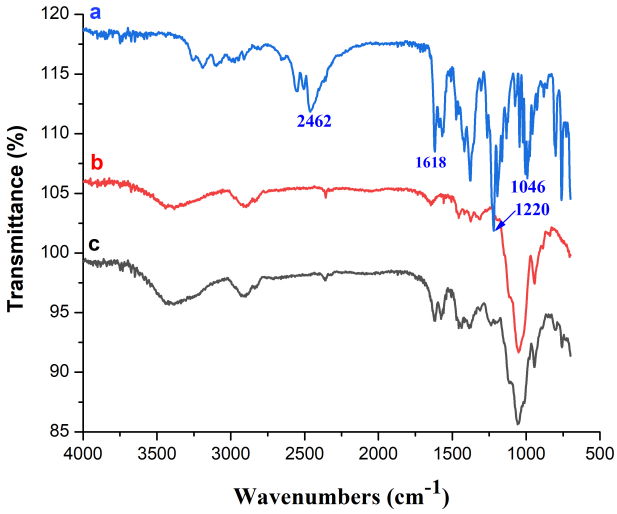

Fig. 3: FTIR of a: pure drug, b: blank and c: drug loaded film (A12).

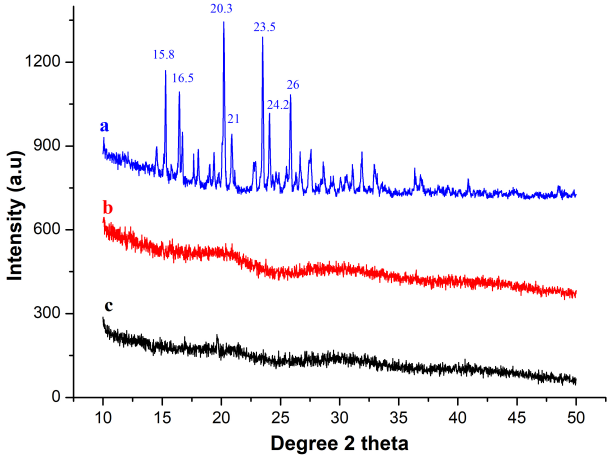

Fig. 4: XRD of a: pure drug, b: blank, and c: drug loaded film (A12).

Characterization of optimized oral film (A12)

Thickness

Thickness is the physical parameter that indicates uniform casting of films. It is directly proportional to the concentration of polymer (Satyanarayana and Keshavarao, 2012). Here, optimized A12 film was 0.041mm thick, which falls within the permitted range i.e. 5-200µm (Lai *et al.*, 2018).

Folding endurance

Folding endurance confirms the flexibility or brittleness of the films and thus useful parameter to ensure handling

Table 1: Selection of optimum superdisintegrating agent

Formulation code	Superdisintegrating agent (% w/w of polymer)	HPMC- E5 (w/v %)	PG (w/w % of polymer)	RHCl (% w/w of polymer)	DT ±SD (Sec)
A1	5% CCS	3%	10%	50%	38.59 ± 1.69
A2	7.5% CCS				36.24 ± 6.04
A3	10% CCS				33.94 ± 7.24
A4	5% SSG	3%	10%	50%	39.07 ± 5.47
A5	7.5% SSG				36.05 ± 5.28
A6	10% SSG				31.73 ± 8.77
A7	5% KT-314	3%	10%	50%	32.66 ± 6.35
A8	7.5% KT-314				30.44 ± 4.56
A9	10% KT-314				27.62 ± 1.34
A10	5% PF	3%	10%	50%	35.38 ± 2.72
A11	7.5% PF				24.37 ± 4.31
A12	10% PF				14.4 ± 1.72

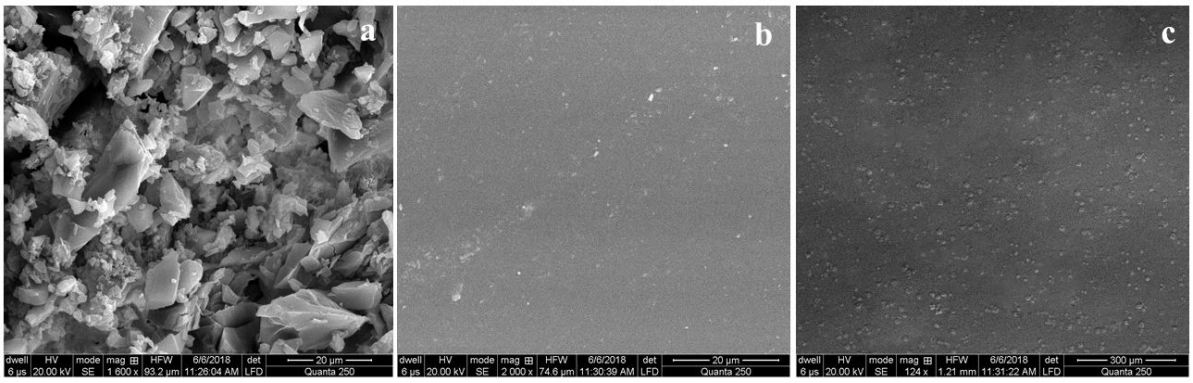

Fig. 5: SEM of a: pure drug, b: blank and c: drug loaded film (A12).

conditions and application (Tejada *et al.*, 2018). Our optimized formulation had folding endurance >300, which is within the permitted limits.

Tensile Strength

Tensile strength of optimized film (A12) was 4.61±0.08 N/mm^2, which specifies the optimum toughness to endure the handling and processing stress.

In vitro disintegration time

In vitro disintegration is an indication of release of drug entrapped in ODF and also marks onset of action for drug (Kumar *et al.*, 2014, Prajapati *et al.*, 2018). The meantime for complete disintegration of the optimized film was 14.4 seconds, which is suitable for rapid onset of action.

Solid-state characterization of A12

Drug-Polymer compatibility

To gain insight on compatibility at the molecular level, pure drug, blank film, and RHCl loaded film (A12) were examined by FTIR as illustrated in fig. 3.

In literature, FTIR spectra of RHCl is characterized by stretching peak of C=N of nitronic acid at 1620 cm^{-1} and two other peaks due to amidine moiety (N−C=N) at 1590 and 1570 cm^{-1} (Chieng *et al.*, 2009). The peak associated with the dimethyl amino group of RHCl appears between 2700 - 2250 cm^{-1} (Gaitano *et al.*, 2016). RHCl occurs in the crystal form I or II and is differentiated by the presence of strong peak at 1046 cm^{-1}, which indicates the crystal form II of RHCl. The FTIR spectra of RHCl in our study (fig. 3a) exhibited C=N of nitronic acid, N−C−C stretching vibration, N−C=N (amidine group), NO_2 (nitro group), $NH(CH_3)_2$ (dimethylamine group), aliphatic C−H stretching, and C−H of furan ring signals at 1618, 1005, 1589, 1220, 2462, 2910, 2949, 2973, 2995, 3014, and 3097 cm^{-1}, respectively. The spectra also showed two distinctive absorption bands of two primer amide groups (N−H) at 3188 and 3256 cm^{-1}, respectively. In blank film (fig. 3b), HPMC E5 showed peak at 1047 cm^{-1}, which is due to stretching of C−O group (Zaini *et al.*, 2017). In optimized film (A12), peak of crystalline form II of drug was slightly shifted from 1046 to 1050 cm^{-1}.

Crystallinity analysis

Crystallinity of compound is detected by the presence of sharp peaks in XRD, which are not found in amorphous compounds (Mehmood *et al.*, 2020). The XRD analysis was performed to assess the crystallinity of drug before and after loading in film. RHCl depicts its crystalline peaks at diffraction angle (2θ): 15.8˚, 16.5˚, 20.3˚, 21˚, 23.5˚, 24.2˚ and 26˚ as shown in fig. 4a. Blank film

presented diffused peaks (fig. 4b) Similarly; XRD pattern of A12 did not showed crystalline peaks of RHCl (fig. 4c).

Surface morphology

SEM photpgraphs were used to asses the morphology of pure drug, blank and optimized drug loaded films (A12). SEM results depict that pure drug was in crystalline form as illustrated in fig. 5a. SEM of blank and loaded (A12) film is illustrated in fig. 5b & c, which shows uniform, smooth surface without any folds or cracks.

In vitro release profile

In vitro release profile of optimized film containing 97.7% of drug was performed in pH 6.8 as illustrated in fig. 6. The result indicates that the 81% of drug was released within two minutes while the remaining drug released within six minutes.

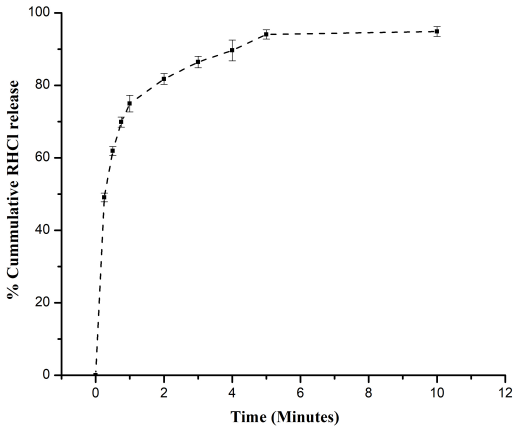

Fig. 6: Release profile of RHCl from ODF A12. Error bars represents ±SD (n=3)

DISCUSSION

Selection of optimized oral film

RHCl is H_2 receptor antagonist and is widely used to treat hyperacidity conditions. Its oral bioavailability is less than 50% due to its short half-life (2.2h), intestinal degradation, poor absorption and hepatic metabolism. Therefore, development of ODF is need of time. HPMC E5 was used for development of ODF of RHCl due to its low viscosity and rapid disintegration in dissolution media. Here, thickness of ODF increased proportionally to the concentration of HPMC E5 (fig. 1a) and is in agreement with Prabhu *et al.* (2011) who reported that increased concentration of polymer had positive effect on thickness of films. PG was selected as plasticizer to give it sufficient flexibility to withstand different stresses encountered during transportation, storage and handling. PG enhanced appearance and flexibility of film, probably by decreasing the tensile strength (Sayed *et al.*, 2013) as compared to PEG 400 and GLY (fig. 1b). Polymer concentration also affected folding endurance. HPMC E5, 3% w/v showed best results for folding endurance which, indicates that film was durable and flexible (fig. 1b) and is in agreement with results of Singh *et al.* (2018) who developed frovatriptan loaded fast dissolving films for management of migraine using composite films of HPMC. The results demonstrated that PG played key role in decreasing the DT, probably by decreasing the tensile strength (Sayed *et al.*, 2013). Increasing the concentration of HPMC E5 had negative impact on DT (fig. 1c). It is reported that as the concentration of polymer is increased, the DT of film is also increased. The probable reason could be due to formation of thick viscous gel barrier of polymer at higher concentration, which hinders the further penetration of fluid into deeper layers and delays the disintegration time of oral film (Satyanarayana and Keshavarao, 2012, Singh *et al.*, 2018, Xu *et al.*, 2014).

Among the different plasticizers used for development of ODF, PG showed significant plasticizing effect that may be due to following facts. a) It is homogeneously dispersed among the polymer chains and makes films flexible and transparent as reported previously (Jagadeesh *et al.*, 2013). b) Due to its negative heat of solution and imparting mechanical strength to films. Moreover, this negative heat of solution also imparts cooling effect in the mouth, which is very desirable (Sayed *et al.*, 2013). On the other hand, among the different concentration of HPMC E5 evaluated, 3% w/v showed best results with formation of transparent, smooth, flexible oral film, with optimum thickness without stickiness or brittleness having optimum DT and thus was favorable for the development of ODF.

CCS, SSG, KT-314, and PF were used at three different levels as superdisintegrants. In the ODF containing CCS, SSG, and KT 314, films were opaque (fig. 2) and their DT was higher compared to the film containing PF (table 1). This is because CCS and SSG are partially soluble in water, and KT 314 (weakly acidic cation exchange resin) only disperses in water as it is practically insoluble in water (Rowe *et al.*, 2009). Here, A12 was considered optimum formulation having PF as a superdisintegrating agent with a minimum disintegration time (14.4 sec), crystal clear appearance, smooth surface, good endurance and flexibility (Manda *et al.*, 2018, Singh *et al.*, 2018) as illustrated in fig. 2 and table 1. PF was used as RHCl release modifier and is mainly composed of mannitol and starch. Here, mannitol also gives cooling sensation due to negative heat of solution and additionally has a sweet taste, which improves the oral film palatability (Manda *et al.*, 2018). These results are in accordance with Mashru *et al.* (2005) who used mannitol as superdisintegrant where by increasing its concentration, the disintegration time decreased and enhanced the percent drug release from the film. Therefore, after detailed screening, A12 was selected as optimized formulation and carried for further testing.

Characterization of optimized oral film (A12)

Optimized films were thin and of uniform thickness. It is reported that thick films delay disintegration while too thin films are damaged during peeling (Preis *et al.*, 2013). Folding endurance of A12 was >300, which is within the permitted limits. It is reported that films surviving 300 or >300 folds shows excellent film endurance, between 200 - 300 show good endurance, while average films exhibit folding endurance less than 200 and lastly, poor films show brittleness or non-continuous pattern thus have poor folding endurance (Chandra *et al.*, 2018). This shows developed films are of sufficient strength for future handling till it consumed by patient.

Tensile strength of ODF depicts the strength and toughness of the film (Bharti *et al.*, 2019). An oral film should possess moderate tensile strength (Takeuchi *et al.*, 2020), as too rigid film not only feels bad in mouth but is also weak (Bharti *et al.*, 2019). Satyanarayana and Keshavarao (2012) developed anastrozole loaded oral film of HPMC E5 with a tensile strength of 4.51 ± 0.09 N/mm^2 and (Takeuchi *et al.*, 2020) reported HPMC based films containing acetaminophen with tensile strength of 6.4 N/mm^2.

For rapid release of drug fast dissolving systems must disintegrate rapidly. For oral fast disintegrating tablets, DT of 30 seconds or less is deemed suitable according to Center for drug evaluation and research (FDA CDER) guidelines and can equally be applied for ODF (Dixit and Puthli, 2009).

Solid state characterization of optimized oral film (A12)

FTIR is frequently used to assess the compatibility between drug and excipients in newly developed formulations. In FTIR spectra of RHCl, strong peak was observed at 1046 cm^{-1}, which depicts crystalline form II of RHCl. This is in good agreement with previously published spectrum of the drug (Gaitano *et al.*, 2016). The crystal form I, is less stable and does not show peak at this wavelength (Sarisuta *et al.*, 2006). Moreover, characteristic peaks for form II of RHCl slightly shifted from 1046 to 1050 cm^{-1} in optimized formulation, which may be due to overlapping of crystalline peak with C−O group peak of HPMC (Jung *et al.*, 2008, Sarisuta *et al.*, 2006) as shown in fig. 3c. Thus, FTIR study indicates the absence of drug polymer interaction. XRD is used to detect the crystalline or amorphous state of drug. Pure RHCl was crystalline in nature and is in line with previously observed data (Gaitano *et al.*, 2016). Blank film presented diffused peaks (fig. 4b) that could be due to amorphous nature of HPMC E5 and other excipients (Sayed *et al.*, 2013). A12 also presented diffused peaks that indicates dispersion of RHCl in molecular or amorphous state within the film (Chandra *et al.*, 2018). SEM revealed crystalline nature of RHCl and further confirming XRD results. SEM showed uniform distribution of its constituents without any visible signs of agreggation (fig. 5c) thus could make formulation more stable and later on ensures accuracy of dose.

In vitro drug release

Optimized formulation (A12) released 81% of the drug within two minutes. The fast release of drug from the film is attributed to presence of superdisintegrating agent (PF), which creates channels upon contact with dissolution media. This facilitates water penetration into polymer matrix, as a result, polymer chains are disentangled and drug diffuses into dissolution media (Hifumi *et al.*, 2016). Another contributing factor for rapid release could be the presence of RHCl in amorphous state as confirmed by XRD and SEM. It is fact that amorphous state of drug leads to high-energy state, which enhances the solubility and dissolution rate (Jermain *et al.*, 2018, Tejada *et al.*, 2018). Similar results were reported by (Mushtaque *et al.*, 2020) they developed oral fast dissolving thin film of escitalopram using HPMC as film matrix. Films released 90% of its contents within first two minutes.

To summarize all formulation ingredients of optimized ODF show good compatibility with RHCl, uniform distribution of drug in film, and rapid drug release within short period. Therefore, ODF A12 is expected to readily disperse in saliva followed by rapid systemic absorption from oral cavity and thus it will avoid the intestinal and pre-systemic hepatic metabolism of RHCl. Moreover, it will be more convenient for old aged patients or one suffering from swallowing issues. Lastly, as these films are produced using simple, reproducible method with tendency for easy scale up. Thus are capable to fulfill the need of the commercial scale manufacturing.

CONCLUSION

Here, after detailed preformulation studies, 3% w/v HPMC E5 as a polymer, PF as a release modifier and PG as a plasticizer were found suitable to develop optimized ODF (A12) of RHCl with adequate physico-mechanical properties i.e. folding endurance >300, disintegrating time < 15 sec, and more than 81% of drug released within two minutes. The results of FTIR, XRD, and SEM analysis revealed that the drug was compatible with other film forming excipients, and uniformly dispersed in amorphous state. Therefore, ODF A12 was stable and released maximum drug in short period. ODF will be a good alternative carrier for enhancing RHCl systemic availability. Moreover, can be conveniently used in elderly patients or one suffering from swallowing issues.

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