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Effect of synthetic super disintegrants and natural polymers in the preparation of donepezil hydrochloride fast disintegration films

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ABSTRACT
The main aim of the present research was to develop a fast dissolving oral polymeric film with good mechanical properties, faster disintegration and dissolution when placed on tongue. Donepezil hydrochloride (DPH) is prescribed in the treatment of mild to moderate Alzheimer's disease (AD). The polymers selected for preparing films were sodium alginate (SA), poly vinyl alcohol (PVA) and guar gum (GG). Three batches of films were prepared by solvent casting method with sodium alginate, sodium alginate & PVA and with the combination of sodium alginate & guar gum. From these three batches, three optimized film formulations S3, SP7 and SG8 were selected based on disintegration time. To these three selected film formulations, superdisintegrants sodium starch glycolate (SSG), cross carmellose sodium (CCS) and cross povidone (CP) were added at a concentration of 4% w/w of polymer to improve the disintegration time. The films prepared with or without superdisintegrants were compared for fast releasing properties. Based on DT and *in vitro* dissolution data, S3CP was selected as the best formulation among the all formulations.

Key Words: Fast dissolving oral disintegration films, donepezil hydrochloride, super disintegrants, natural polymer.

INTRODUCTION

Alzheimer's disease is a disease of neuro degeneration of the central nervous system characterized by premature senile mental deterioration. Alzheimer's disease patients show marked decrease in cognitive ability and severe behavioral abnormalities such as anxiety, depression, irritability, disorientation and restlessness (Sugimoto, 1999). People of old age are subjected to this disease prevalently. Donepezil hydrochloride is the choice of drug for mild to severe Alzheimer's disease (Tsuno, 2009).

Over the past decades, there has been an increased research for novel drug delivery systems (NDDS) to improve safety, efficacy and patient compliance. The discovery of new chemical entity is highly expensive and time consuming, hence pharmaceutical industries are focusing on the design and development of new drug delivery systems for existing drugs leading to better bioavailability, reduced adverse effects and with more patient compliance (Rathi varun *et al.*, 2011).

Patient compliance is an important aspect while considering a formulation of NDDS. Oral thin film (OTF) is one of such novel technologies (Srikanth *et al.*, 2011). OTF provides a convenient means of administration of drugs. They are the alternative to oral dispersible tablets. The oral thin films are the best choice of dosage forms for pediatric, geriatric population, dysphasic patients; patients suffer from sore throat, finds difficulty in swallowing the tablet dosage form.

In the present study three hydrophilic polymers i.e. sodium alginate, guar gum and poly vinyl alcohol have been used in different combinations to optimize the formulation. Three super disintegrants i.e. sodium starch glycolate, cross carmellose sodium and cross povidone were used to decrease the disintegration time of formulations to enhance faster disintegration time.

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MATERIALS AND METHODS

Donepezil hydrochloride was collected from Dr. Reddys Laboratories, Hyderabad. Sodium alginate, poly vinyl alcohol, guar gum, sodium starch glycolate, cross carmellose sodium and cross povidone were purchased from SD Fine-Chem. Limited, India. All the reagents and chemicals used were of analytical grade.

Dose calculations of the drug

Diameter of the plate = 6 cm
Area of the plate = 28.6 cm^2
Number of 4 cm^2 films obtained in the whole teflon plate = 28.6/4 = 7.065
Each film contains 5 mg of drug
7.065 films contain 35.325 mg of drug
The amount of drug added in each plate = 36 mg (approximately).

Solvent casting method was used for this formulation. Excipients used were sodium alginate (SA), poly vinyl alcohol (PVA), guar gum (GG), sodium starch glycolate (SSG), cross carmellose sodium (CCS) and cross povidone (CP).Initially placebo (drug free) films were prepared with different polymers alone and their combinations to optimize the concentration of polymers and concentration of plasticizer to be used. In all the cases, glycerin was used as plasticizer in the concentration of 10% of polymer weight based on the characteristics of the films obtained. Then oral thin films were prepared by using sodium alginate, sodium alginate PVA and sodium alginate guar gum combinations.

Three best formulations were selected from the above three batches of formulations based on their disintegration times. Further batch of formulations were prepared in combination with the super disintegrants. Films were prepared using sodium starch glycolate (SSG), cross carmellose sodium (CCS) and cross povidone (CP) at 4% w/w of polymer in addition to other ingredients of the original formulation as represented in table 1.

Table 1: Formulation of films.

No. of Runs	Trial code	SA (mg)	PVA (mg)	GG (mg)	SSG (mg)	CCS (mg)	CP (mg)
1	S3SSG	200	-	8	-	-	-
2	S3CCS	200	-	-	-	8	0
3	S3CP	200	-	-	-	-	8
4	SP7SSG	200	100	-	12	-	-
5	SP7CCS	200	100	-	-	12	-
6	SP7CP 200	100	-	-	-	12	-
7	SG8SSG	150	-	150	12	-	-
8	SG8CCS	150	-	150	-	12	-
9	SG8CP	150	-	150	-	0	12

Note: DPH 36 mg, glycerin 10% w/w of polymer and aspartame 20 mg are common for all formulations.

Preparation of oral films

Films with super disintegrants were prepared by adding weighed amount of super disintegrants in the polymeric solution in addition to drug mannitol, aspartame and glycerin. The obtained solution was stirred continuously for 15-20 minutes to get bubble free solution this solution was kept aside for some time. These solutions were slowly casted with a continuous flow on teflon plate of diameter 6 cm in order to avoid bubble formation. The plates were kept in hot air oven at 40°C for 24 hrs. The formed film was taken out after 24 hrs from hot air oven and checked for its complete dryness. The dried film was gently separated from the teflon plate and cut into individual films of area 4 cm^2 (2cm*2cm). The films were preserved by wrapping in aluminium foil and used for evaluation tests further.

Evaluation of DPH oral films

1. Visual inspection & film formation (Ciluzo *et al*., 2008)
The film was evaluated visually for its clarity, transparency and stickiness. If it was satisfactory, then it was taken for further evaluation. If the formed films were not satisfactory they were discarded.

2. Weight variation (Sapkal *et al.*, 2011)
This test ensures the uniformity of the formed film. From the whole film three small pieces work at randomly, each of 1 cm^2 (1 cm*1 cm) area and were weighed individually. The standard deviation from the mean value was reported.

3. Folding endurance (Vishwakarma *et al*., 2011)
Determination of folding endurance of the film was done by folding a small strip of film (2 cm* 2 cm) at the same place repeatedly until it broke. The no. of times the film could be folded at the specific place without breaking gives the folding endurance value.

4. Content uniformity (Shinde *et al*., 2008)
The content uniformity test is used to ensure that every film contains the same amount of drug substance intended with little variation among films within the whole film. From the whole film, 3three pieces were cut, each of area 4 cm^2 (2 cm* 2 cm) and assayed for the drug content. Uniformity of content was reported by measuring the mean and standard deviation values.

5. Potency determination (Patel *et al.*, 2009)
The drug assay was performed to ensure proper drug loading in each film. Assay was performed by taking out a 4 cm^2 (2 cm * 2 cm) area of film from the whole film. It was dissolved in 50 ml of pH 6.8 phosphate buffer with the aid of stirring. This solution was filtered by using Whattmann filter paper, the filtrate was diluted to with the same buffer up to 100 ml in volumetric flask. The solution was analyzed in double beam UV spectrophotometer at a wavelength of 230 nm, which is the λmax of DPH against the blank. This test was performed in triplicates with three different films to ensure reproducibility.

6. Thickness test (Mahesh *et al*., 2010)
The film thickness was measured by using micrometer screw gauge at five points (centre and four corners) on the film to make sure that the film thickness is uniform throughout. From the five points, mean thickness was calculated. Samples with air bubbles, nicks or tears were excluded from analysis. The standard deviation from the mean value was reported.

7. *In vitro* disintegration test
Two simple methods can be used to measure disintegration time. In the first method, one drop of pH 6.8 Phosphate buffer is dropped from a 10 ml pipette onto the tightly clamped film strip. The time taken to make a hole through the film is to be measured and noted down as the disintegration time (Mishra and Amin, 2011).

In the second method, 5 ml of pH 6.8 phosphate buffer was taken in a petri plate and the film was placed on the surface of it. The time taken for disintegration of the film was measured as the disintegration time. This test was followed in the present study, evaluation was done in triplicates and the standard deviation from the mean value was reported (Mihir *et al*., 2012).

8. Surface pH
1 cm^2 film of each formulation was taken and it was placed in a petri plate containing 1 ml of water. After wetting of the film, the surface pH of the film was checked by using pH electrode. all these results are represented in table 2.

9. *In vitro* Dissolution (Dinge and Nagarsenkar, 2008)
In the previous studies, dissolution study for the films was carried out using USP apparatus 5, *i.e.* Paddle over

Table 2: Evaluation tests results.

Formulation	Weight variation (mg) Mean±SD	Content uniformity (mg) Mean±SD	Thickness (µm) Mean±SD	Folding endurance	Assay	Disintegration time
S3SSG	62.67±0.57	4.93±0.03	124±5.52	148	98.6	11.67±0.57
S3CCS	62.67±1.52	5.03±0.06	124±8.36	155	100	11.00±1.00
S3CP	62.33±1.52	4.93±0.18	118±2.47	143	98.6	10.33±0.57
SP7SSG	63.67±1.52	4.92±0.12	130±8.36	145	98.4	16.33±1.52
SP7CCS	63.67±0.57	5.01±0.10	126±5.52	152	102	15.00±1.00
SP7CP	63.00±1.00	4.84±0.12	124±5.52	156	96.8	13.67±0.57
SG8SSG	64.67±0.57	4.92±0.06	136±7.72	140	98.4	20.00±1.00
SG8CCS	64.00±1.00	4.84±0.12	130±0.00	158	96.8	18.33±0.57
SG8CP	63.33±0.57	4.85±0.18	124±5.47	140	97	14.67±0.57

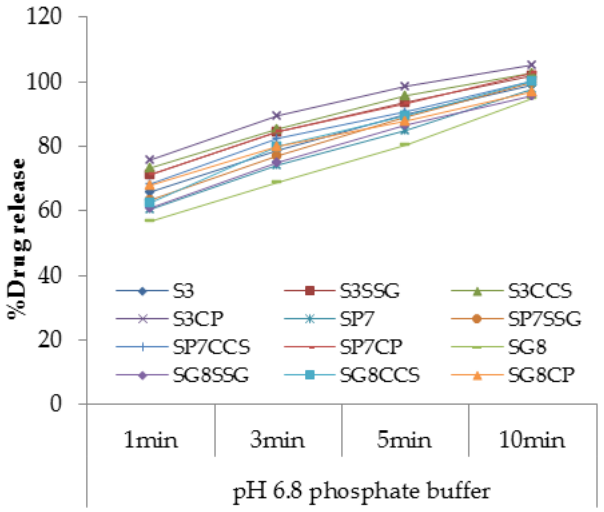

Figure 1: ***In vitro*** **drug release in 6.8 pH phosphate buffer.**

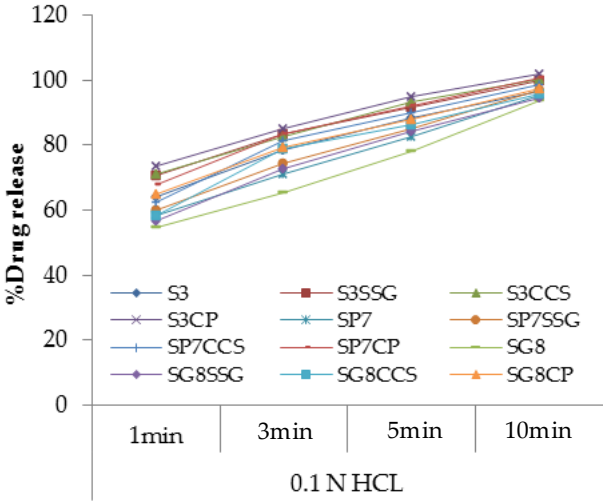

Figure 2: ***In vitro*** **drug release in 0.1N HCl.**

disc method. In the present study, as the Paddle over disc apparatus is not available, USP apparatus II (paddle) was used.

A. In vitro dissolution in phosphate buffer pH 6.8

It was carried out in 900ml of simulated saliva solution, which consists of phosphate buffer saline solution at 37°C was used as the dissolution medium. Simulated saliva was prepared by dissolving 2.38 gm of Na_2HPO4, 0.19 gm of KH_2PO4 and 8 gm of NaCl in 1000 ml of distilled water. pH of the resulting medium was adjusted to 6.8 using Phosphoric acid. The temperature of the medium was maintained at 37±0.5°C. The apparatus was set at 50 rpm. A film sample of 4 cm^2 (2 cm x 2cm) was cut and taken into the basket. 5 ml of samples were taken at 1, 3, 5, 10 min time points and the same amount of the dissolution medium was added to maintain sink conditions throughout the dissolution. The withdrawn samples were filtered using Whattmann filter paper and analyzed using double beam UV spectrophotometer at a wave length of 230 nm. The percentage release of drug was calculated by using standard graph of DPH in pH 6.8 phosphate buffer. The dissolution study was performed in triplicates and the average values of percentage releases were taken. Time vs. percentage drug release plots were drawn to know where the maximum amount of drug was released. Dissolution studies were conducted for optimized formulations only.

B. In vitro dissolution in 0.1 N HCl

It was carried out in 900 ml 0.1 N HCl in same way as that of the ODTs. The temperature of the medium was maintained at 37±0.5°C. The apparatus was set at 50 rpm. A film sample of 4 cm^2 (2 cm x 2cm) was cut and taken into the basket. 5 ml of samples were taken at 1, 3, 5, 10 min time points and the same amount of the dissolution medium was added to maintain sink conditions throughout the dissolution.

The withdrawn samples were filtered using Whattmann filter paper and analyzed using double beam UV spectrophotometer at a wave length of 230.4 nm. The percentage drug release of drug was calculated by using standard graph of DPH in 0.1 N HCl. The dissolution study was performed in triplicates and the average values were taken. Time vs. Percentage drug release plots were drawn to know where the maximum amount of drug was released. Dissolution studies were conducted for optimized formulations only.

RESULTS AND DISCUSSION

The film formulations prepared were clear and transparent without air bubbles, non-greasy to touch, smooth and flexible. The films have shown a maximum percent weight variation of less than 5%. And the formulations have shown a good folding endurance (Vishwakarma *et al.*, 2011) of about 150.The drug was found to be distributed uniformly throughout the film. The percent standard deviation was in the range of 0.5 to 4% (Shinde *et al.*, 2008). The assay values for all the films were in the range of 94-104% (Patel *et al.*, 2009). The average film thickness (Mahesh *et al.*, 2010) was varying from 110-140 µm, the best disintegrating time was reported for the film formulation S_3CP, which was disintegrated in 10.33 sec, the pH range was found to be 6-7, which is acceptable, the results are represented in table 2.

In vitro dissolution studies for optimized films

Based on disintegration time, twelve best film formulations *i.e.* 3 formulations from film formulations prepared by using sodium alginate, sodium alginate and PVA, sodium alginate and guar gum, remaining 9 formulations prepared by using three different super disintegrants for each of these S3, SP7 and SG8. The formulations selected for *in vitro* drug release studies were S3, S_3SSG, S_3CCS, S_3CP, SP7, SP_7SSG, SP_7CCS, SP_7CP, SG8, SG_8SSG, SG_8CCS and SG_8CP.

In vitro dissolution study in pH 6.8 phosphate buffer

S3CP has shown the highest amount of drug release of 98.74% within 5 min.

In vitro dissolution study in 0.1 N HCl

S3CP has shown the highest amount of drug release of 94.92% within 5 min. From the results, cross povidone shows good disintegrating property in all the cases among the three super disintegrants used for the study, *in vitro* drug release results are represented in figures 1 and 2.

CONCLUSION

Donepezil hydrochloride fast dissolving oral films were prepared using water soluble polymers and sodium alginate, PVA and guar gum by solvent casting technique. Film formulations prepared by using super disintegrants (SSG, CCS and CP) have shown less disintegration time compared to that of the films prepared without super disintegrants. Least disintegration time of 10.33 sec was observed for the formulation S3CP. It has shown 89.46% drug release within 3 min in pH 6.8 phosphate buffer and >90% drug release within 5 min in both the media. DPH fast dissolving oral films were prepared successfully with fast disintegration using film forming polymer sodium alginate and super disintegrants cross povidone. S3CP was the best amongst all the formulations in the present study.

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