FORMULATION AND EVALUATION OF MUCOADHESIVE BUCCAL FILM OF SAXAGLIPTIN HYDROCHLORIDE

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- **ABSTRACT**

Buccal route is an attractive route of administration for systemic drug delivery and it leads direct access to the systemic circulation through the internal jugular vein by passes drugs from the hepatic first pass metabolism provides high bioavailability. Buccal bioadhesive films, releasing topical drugs in the oral cavity at a slow and predetermined rate, provide distinct advantages over traditional dosage forms for treatment of many diseases. This article aims to review the recent developments in the buccal adhesive drug delivery systems to provide basic principles to the young scientists, which will be useful to circumvent the difficulties associated with the formulation design

- **Introduction of Buccal Drug Delivery System**

A drug can be administered via a many different routes to produce a systemic pharmacological effect. The most common method of drug administration is via per oral route in which the drug is swallowed and enters the systemic circulation primarily through the membrane of the small intestine. The oral route of drug administration is the most important method of administering drugs for systemic effect. The parenteral route is not routinely used for self–administration of medication. It is probable that at least 90 % of all drugs used to produce systemic effects are administered by the oral route. Absorption of drugs after oral administration may occur at the various body sites between the mouth and rectum.

In general, the higher up a drug is absorbed along the alimentary tract, the more rapid will be its action, a desirable feature in most instances. A drug taken orally must withstand large fluctuation in pH as it travels along the gastrointestinal tract, as well as resist the onslaught of the enzymes that digest food and metabolism by micro flora that live there. It is estimated that 25%

of the population finds it difficult to swallow tablets and capsules and therefore do not take their medication as prescribed by their doctor resulting in high incidence of non-compliance and ineffective therapy. Difficulty is experienced in particular by pediatrics and geriatric patients, but it also applies to people who are ill bedridden and to those active working patient who are busy or travelling, especially those who have no access to water. In these cases oral mucosal drug delivery is most preferred.

It has been known for centuries that buccal and sublingual administration drug solutes are rapidly absorbed into the reticulated vein, which lies underneath the oral mucosa and transported through the facial veins, internal juglar vein, and brachiocephalic vein and are then drained into the systemic circulation. Therefore the buccal and sublingual routes of administration can be utilized to bypass the hepatic first-pass elimination of drugs. Within the oral mucosal cavity, the buccal region offers an attractive route of administration for systemic drug delivery. The mucosa has a rich blood supply and it is relatively permeable. The oral cavity is highly acceptable by patients, the mucosa is relatively permeable with a rich blood supply and the virtual lack of langerhans cells makes the oral mucosa tolerant to potential allergens.

- **Oral mucosal sites:**

Within the oral mucosal cavity, delivery of drugs is classified in to three categories.

1. **Sublingual delivery:** is the administration of the drug via the sublingual mucosa (the membrane of the ventral surface of the tongue and the floor of the mouth to the systemic circulation.
2. **Buccal delivery:** is the administration of drug via the buccal mucosa(the lining of the cheek)to the systemic circulation.
3. **Local delivery:** for the treatment of conditions of the oral cavity, principally ulcers, fungal conditions and periodontal disease. These oral mucosal sites differ greatly from one another in terms of anatomy, permeability to an applied drug and their ability to retain a delivery system for a desired length of time.

Oral mucosa

The oral mucosa is composed of an outermost layer of stratified squamous epithelium (about 40-50 layers thick), a lamina propria followed by the sub mucosa as the innermost layer. The composition of the epithelium varies depending on the site in the oral cavity. The mucosa of the gingival and hard palate are keratinized similar to the epidermis contain neutral lipids like ceramides and acylceramides which are relatively impermeable to water. The mucosa of the soft palate, the sublingual, and the buccal regions, however, are not keratinized contain only small amounts of ceramides.

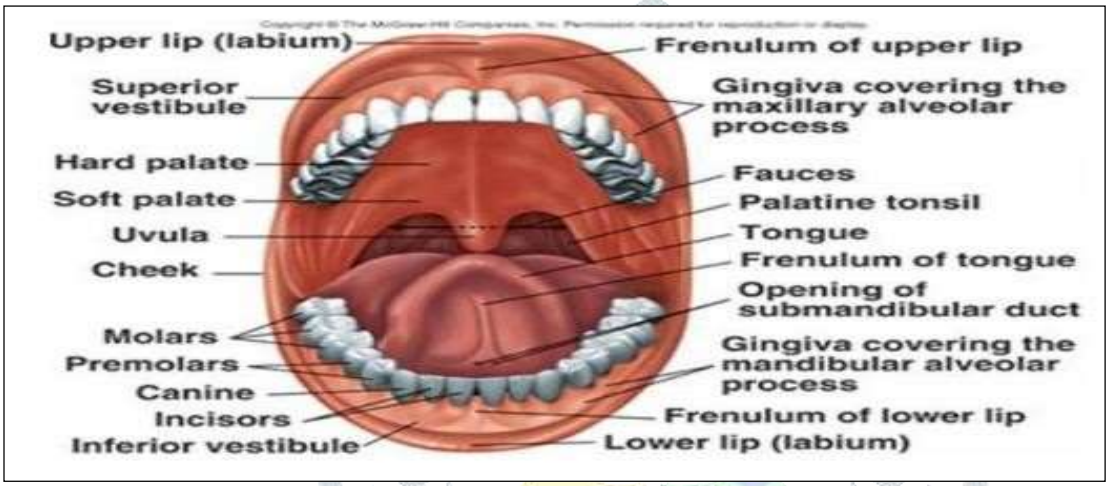
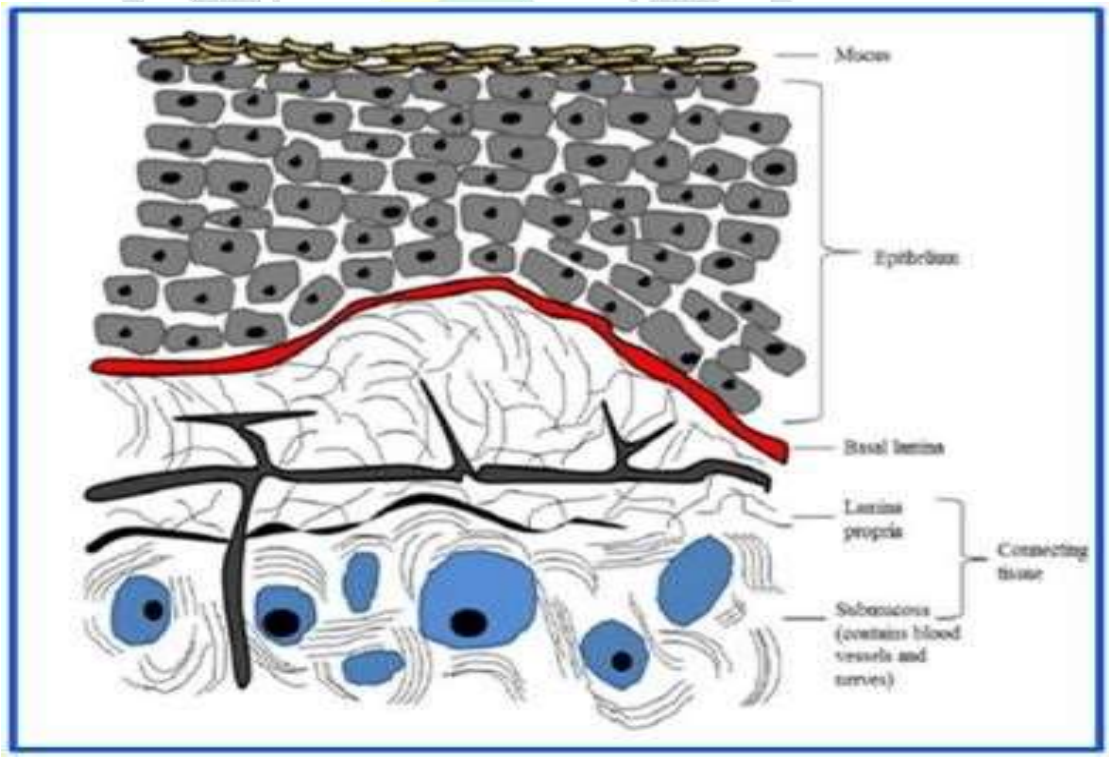


Figure 0:1 Oral cavity



Structure of Buccal Mucosa

Formulation table for Trial batches

Ingredients (mg/Patch)	F1	F2	F3	F4
Saxagliptin HCl	40	40	40	**40**
HPMC E15M	150	100	100	**100**
Sodium CMC	-	50	-	**-**
Carbopol 934 P	-	-	50	**-**
Eudragit RL 100	-	-	-	**50**
Aspartame	5	5	5	**5**
Propylene Glycol (ml)	0.5	0.5	0.5	**0.5**
Ethanol (ml)	20	20	20	**20**

- **Evaluation of Buccal Patches**

Weight Variation/Film Weight:

For evaluation of film weight three films of every formulation were taken and weighed individually on a digital balance. The average weights were calculated.

Thickness:

Three films of each formulation were taken and the film thickness was measured using Vernier calliper at three different places and the mean value was calculated.

Surface pH of films:

The surface pH of all formulations was determined to check whether each film causes irritation to the buccal mucosa. To measure the surface pH of prepared buccal patches, they were kept in 5 ml distilled water for 10 min to swell. After complete swelling, the surface pH was measured by pH meter. pH probe was in contact with the surface of each film and was allowed to equilibrate for 1 min. The average values are reported.

Folding endurance:

Three films of each formulation of size (1 × 1 cm) were cut by using sharp blade. Folding endurance was determined by repeatedly folding a small strip of film at the same place till it

broke. The number of times, the film could be folded at the same place without breaking gave the value of folding endurance. The mean value of three readings and standard deviation were recorded.

Swelling ratio (%)

After calculating the primary weight of 1 × 1 cm^2 film (W1), the swelling properties of films was determined by placing films in PBS (pH 6.8) at 37 °C. At specified time interval (2 hour) of films were removed from PBS solution and excess PBS was removed with filter paper until the films degraded. The swollen films were weighed (*W* 2) and swelling ratio was calculated using following equation;

$$\textbf{Swelling (\%)} = (w1-w2)/\ w1\times 100$$

Drug content

Three Films were cut into 1 × 1 cm^2 pieces and placed in a solution of 100 ml pH 6.8 phosphate buffer. Dissolve the films completely and filtered through whatman filter paper. The solution was checked using UV spectrometry method at 212 nm wavelength. The average of drug contents of three films was taken as final reading.

***In vitro* drug release study**

USP Type-2 rotating paddle dissolution test apparatus was used to study the dissolution profile of buccal patches). The dissolution medium used was 250 ml 6.8 phosphate buffer at 37 ± 0.5 °C which was stirred at 50 rpm. The patch of 1 X 1 cm^2 diameter was fixed on the glass disk with the help of a cyanoacrylate adhesive. The disk was put at the bottom of the dissolution vessel so that the patch remained on the upper side of the disk. Samples (5 ml) were withdrawn at pre-determined time intervals (30, 60, 90, 120, 150 and 180 min) and replaced with equal volume of dissolution medium. The samples were filtered through 0.45 µm filter and appropriately diluted with 6.8 phosphate buffer and assayed spectrophotometrically at 212 nm.

Drug Release Kinetic Study

Data obtained form in vitro drug release studies were fitted to disso calculation software. The kinetic models used are zero order, first order, Korshmers and Pepps, Hexon crowell and Higuchi equation.

The rate and mechanism of release of drug from the prepared formulation were analyzed by fitting the dissolution data into the zero-order equation: **Q = k0t**

Where, Q is the amount of drug released at time t, k0 is the release rate constant.

The dissolution data fitted to the first order equation: **ln (100–Q) =**

ln 100 – K1 t Where, k_1 is the release rate constant.

The dissolution data was fitted to the Higuchi's equation: **Q = K2**

t1/2 Where, k_2 is the diffusion rate constant.

The dissolution data was also fitted to Korsmeyer equation, which is often used to Describe the drug release behavior from polymeric systems:

$$\mathbf{Log\ (Mt/M\infty) = log\ k + n\ log\ t}$$

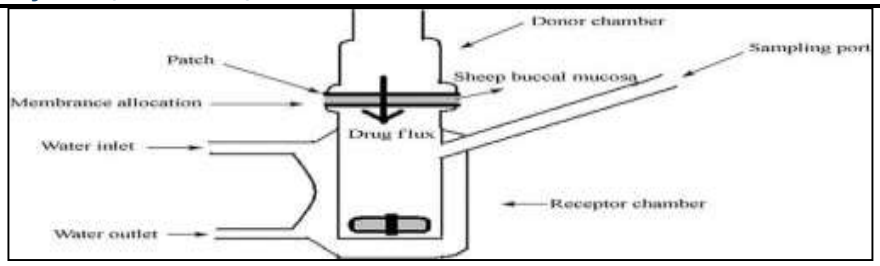
Where Mt is the amount of drug released at time t, M∞ is the amount of drug release

After infinite time, K is a release rate constant incorporating structural and geometric Characteristics of the tablet, n is the diffusional exponent indicative of the mechanism of drug release.

In vitro drug permeation

The *in vitro* buccal permeation of films was studied through the sheep buccal mucosa using Franz-diffusion cell. Freshly obtained buccal mucosa was mounted between the donor and receptor compartments so that the smooth surface of the mucosa faced the donor compartment. The patch was placed on the mucosa and the compartments clamped together. The donor compartment was slightly wetted with 1 mL of phosphate buffer. The receptor compartment was filled with phosphate buffer pH 6.8. The diffusion cell was thermo stated at 37 ± 0.2 °C and the receptor compartment was stirred at a rate of 100 rpm. One millilitre sample was withdrawn at pre-determined time intervals using a butterfly canula and syringe. The buffer was immediately replaced using blank pre-warmed buffer. After filtration through

0.45 µm filter and appropriate dilution the samples were analysed for the drug content spectrophotometrically at 212 nm.



Schematic representation of the modified Franz diffusion cell

Ex vivo mucoadhesion time

A locally modified USP disintegration apparatus was used to determine the *ex vivo* mucoadhesion (residence) time. The mucosal membrane (fresh sheep buccal mucosa) was separated by removing the underlying fat and loose tissues. The membrane was washed with distilled water and then with 6.8 phosphate buffer at 37 °C. Pig cheek mucosa, 4 cm long, was glued to the surface of a glass slide. One side of the patch was wetted with one drop of 6.8 phosphate buffer and pasted to the sheep buccal mucosa by applying a light force with fingertip for 20 s. The glass slide was vertically fixed to the apparatus and allowed to move up and down so that the patch was completely immersed in the buffer solution at the lowest point and was out at the highest point. The beaker was filled with 800 mL of 6.8 phosphate buffer and was kept at 37 ± 1 °C. The time required for the patch to detach from the buccal mucosa was recorded as the mucoadhesion time.

In vitro mucoadhesion strength

The mucoadhesive strength of patches was measured in triplicate on a modified physical balance. A piece of sheep buccal mucosa was tied to the mouth of a glass vial filled completely with 6.8 phosphate buffer. The glass vial was tightly fitted in the centre of a beaker filled with 6.8 phosphate buffer at 37±1 °C. Patches were stuck to the lower side of rubber stoppers with glue and the mass (g) required to detach the patches from the mucosal surface was taken as the mucoadhesive strength (shear stress).

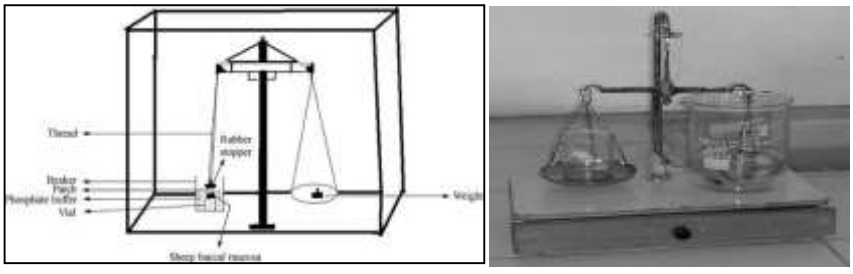


Figure 0:2 Modified physical balance used to measure mucoadhesive strength

Tensile strength and percentage elongation

Tensile Strength is the maximum stress applied to specified part of films without tearing. % Elongation is the maximum deformation of films length without tearing. Film (L_0 initial length, *t* thickness, *w* width) was placed between the clamps lever of instrument, and an extension force at the speed of 2 mm/min was applied to each film. At tearing time, load at failure (*F*) and final length (*L*) was measured. Tensile

Strength and % Elongation were calculated using following equations;

Tensile strength (N/cm^2) =Force x 100/Area

% Elongation = (L-Lo/L) x 100

Results of trial batches F1-F4

Parameters	F1	F2	F3	F4
Appearance	Smooth but thin film	Smooth and flexible	Smooth and Flexible	Smooth and flexible
Weight Variation (mg)	162 ± 2.5	165 ± 3.1	163 ± 1.9	166 ± 2.0
Thickness (mm)	0.24 ± 0.02	0.26± 0.03	0.27 ± 0.01	0.26 ± 0.03
Folding Endurance	136 ± 5.6	195 ± 9.2	203 ± 4.7	218 ± 10.2
Surface pH	6.90 ± 0.05	6.85 ± 0.12	6.70 ± 0.20	6.65 ± 0.25
% Drug Content	97.8 ± 2.6	96.2 ± 1.9	97.3 ±1.5	98.6 ± 1.3
% Swelling (2 hrs)	26.9 ± 2.21	32.5 ± 1.96	15.3 ± 1.10	19.4 ± 1.05
Tensile Strength (N/cm^2)	2.8 ± 0.3	3.5 ± 0.2	3.9 ± 0.3	5.2 ± 0.4

% Elongation	20.3 ± 1.4	32.9 ± 2.0	35.6 ± 1.5	41.8 ± 2.3
Mucoadhesive time (h)	2.35 ± 0.04	3.10 ± 0.03	2.05 ± 0.02	4.15 ± 0.04
Mucoadhesive Strength (g)	9.1 ± 2.4	12.8 ± 3.2	15.6 ± 1.8	25.5 ± 2.5

Analysis of Factorial design: -

The data obtained from the factorial design was fitted in the DOE software and the outcome of the results was recorded below. 2^3 full factorial designs was selected in Design expert 11 software and below data was added to analyze the factorial design.

Table Error! No text of specified style in document.**:1 Data input in DoE Software**

Std Order	Run Order	HPMC E15	Eudragit RL 100	Propylene Glycol	Folding Endurance	Mucoadhesive Strength (g)	% Drug Release at 60 min
8	1	120	75	0.75	323	31.3	39.2
5	2	80	25	0.75	113	16.2	73.2
1	3	80	25	0.25	98	14.3	74.9
6	4	120	25	0.75	213	21.3	61.3
3	5	80	75	0.25	244	23.2	51.2
2	6	120	25	0.25	204	20.4	65.4
7	7	80	75	0.75	260	26.4	45.3
4	8	120	75	0.25	312	28.5	41.0

Drug Release kinetic study was done for factorial batches. The results of drug release data fitted in various kinetic models and the R^2 recorded for every model. The results were recorded below; the most fitted model was first order and higuchi. The 'n' exponent of peppas model was 0.73 suggest fickian diffusion.

Kinetic modeling of factorial batches

Kinetic Model	R^2 value of different model							
	D1	D2	D3	D4	D5	D6	D7	D8
Zero Order	0.9543	0.7815	0.7841	0.8538	0.9129	0.8647	0.9631	0.9708
First Order	0.9811	0.9371	0.9756	0.9983	0.9523	0.8498	0.8874	0.9310
Higuchi	0.9451	0.9451	0.9405	0.9739	0.9584	0.9723	0.9556	0.9429
Peppas	0.9762	0.8794	0.8602	0.9329	0.9566	0.9168	0.9810	0.9812

Ex vivo permeability study of factorial batches was checked and the results were recorded below. The results revealed that the drug release in permeability study was less as compared to the dissolution study. This may be due to the limitation of dissolution medium. All batches showed good permeability and results were found satisfactory. Results were tabulated in table 6.10.

Vivo permeability study of factorial batches

Time (min)	% Permeability (n=6)							
	D1	D2	D3	D4	D5	D6	D7	D8
0	0±0.0	0±0.0	0±0.0	0±0.0	0±0.0	0±0.0	**0±0.0**	0±0.0
30	23.6±3.9	25.9±3.6	28.6±3.1	23.9±3.9	23.1±3.6	20.9±3.6	**22.3±5.2**	20.3±3.4
60	32.9±2.6	36.9±2.8	39.1±3.0	32.9±2.8	40.6±3.0	39.4±3.1	**35.9±4.3**	32.2±2.9
90	48.6±2.1	50.3±2.1	55.9±2.5	45.3±2.4	52.3±2.5	48.6±2.5	**52.1±2.8**	48.3±2.4
120	59.4±1.9	61.9±1.6	63.1±2.3	59.3±1.6	59.3±2.4	60.1±2.1	**74.3±1.9**	54.3±2.1
180	69.2±1.2	72.1±1.1	68.5±2.2	64.3±1.3	71.8±1.9	78.4±2.0	**81.1±1.1**	65.2±1.6

Evaluation parameters of factorial batches

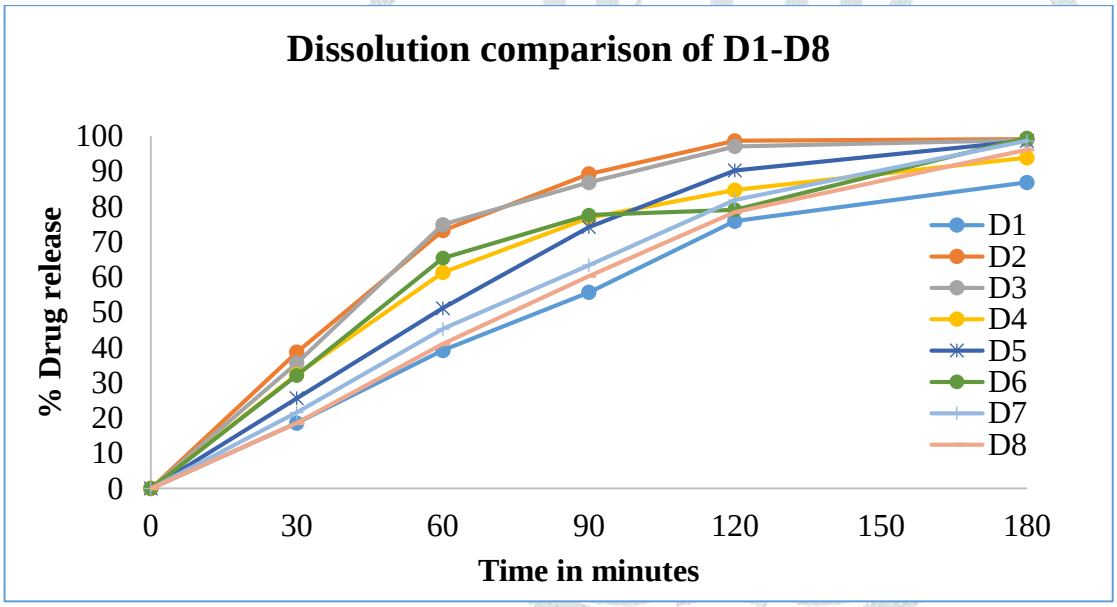
Batch	Tensile Strength (N/cm^2)	% Elongation	Mucoadhesive time (h)	Mucoadhesive Strength (g)
D1	6.9 ± 2.5	53 ± 2.5	4.7 ± 0.02	31.3 ± 1.2
D2	4.3 ± 1.6	32± 3.1	2.5 ± 0.03	16.2 ± 1.0
D3	4.1 ± 1.1	31 ±2.7	2.4 ± 0.01	14.3 ± 1.3
D4	4.8 ± 1.2	38 ± 2.6	4.9 ± 0.02	21.3 ± 1.4
D5	5.3 ± 2.1	42 ± 1.9	3.1 ± 0.01	23.2 ± 1.3
D6	4.9 ± 0.9	37 ± 2.8	4.8 ± 0.03	20.4 ± 1.5
D7	5.4 ± 0.7	41 ± 1.9	3.2 ± 0.02	26.4 ± 1.1
D8	6.8 ± 1.3	54 ± 3.4	4.5 ± 0.01	28.5 ± 0.8

Accelerated stability study

Selected patches were subjected to accelerated stability testing by wrapping them in aluminium foil and packing them in glass vials. These patches were kept at 40°C/ 75% RH for 1 month. The data presented were the mean of three determinations. The patches were examined for changes in appearance, thickness, folding endurance, drug content, surface pH, % swelling and drug release.

Dissolution results of factorial batches

% Drug release (n=6)								
Time (min)	**D1**	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**D8**
0	0±0.0	0±0.0	0±0.0	0±0.0	0±0.0	0±0.0	**0±0.0**	0±0.0
30	18.6±4.3	38.7±1.2	35.6±5.2	32.4±3.4	25.6±3.1	32.1±4.3	**21.6±2.9**	18.6±3.8
60	39.2±2.5	73.2±1.1	74.9±4.1	61.3±4.6	51.2±3.0	65.4±2.4	**45.3±2.7**	41.0±2.9
90	55.7±3.1	89.3±0.8	86.9±3.5	76.8±2.7	74.2±1.9	77.6±2.1	**64.4±2.1**	60.3±2.7
120	75.9±1.9	98.7±0.5	97.1±1.6	84.7±2.2	90.3±1.1	79.1±1.3	**87.9±1.8**	78.5±1.6
180	86.9±0.9	99.2±0.4	98.9±1.1	93.9±1.5	98.1±0.4	97.5±1.1	**98.7±1.4**	96.2±1.4



Dissolution comparison of D1-D8 batch

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