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Design and characterization of Acrylate based Buccoadhesive tablets of Diltiazem hydrochloride

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Abstract: The purpose of this research was to develop and evaluate buccal mucoadhesive controlled release tablets of Diltiazem hydrochloride (DLZ) using interpolymer complex (AAPVP) composed of acrylic acid and poly (vinyl pyrollodone)(PVP) and hydrophilic polymer PVP K-30 in combination. Buccoadhesive tablets were made by direct compression technique and were characterized to evaluate for their technological parameters, content uniformity, swelling behaviour, surface pH, mucoadhesive strength and mechanism of release. *In vitro* release studies were conducted for DLZ-loaded tablets in phosphate buffer (pH, 6.6) solution. Tablets exhibited drug release in the range of 57.6 to 87.8 % in 6 hours. Data of *In vitro* release from tablets were fit to different equations and kinetic models to explain release profiles. Drug release and mucoadhesive strength were found to depend upon proportion of interpolymer complex and PVP K-30. The kinetic results indicates that the release mechanism followed non-fickian diffusion pattern in all formulations indicating the combination of both diffusion and erosion controlled release mechanism (critical value of n = 0.538-0.767). The tablets were found to have sufficient bioadhesion force to adhere to buccal mucosal for the required time.

Keywords: buccal, interpolymercomplex, mucoadhesive, tablets, swelling index

INTRODUCTION

Extensive efforts have been focused at developing mucoadhesive drug delivery systems for an efficient control of systemic delivery [1]. Out of various available mucosal routes, the buccal route has gained significant importance as an alternative to oral route and other mucosal routes because of its attractive advantages and fruitful outcomes. The buccal mucosa has a larger surface area for drug application and has good accessibility as compared to other mucosae such as nasal, rectal and vaginal mucosa [2]. In addition, the buccal mucosa is more tolerant to potential allergant because of its rapid cell turn over [3]. Absorption of therapeutic agents from the oral cavity provides a direct entry of such agents into the systemic circulation, thereby avoiding the first-pass hepatic metabolism [4]. Out of developed mucoadhesive buccal delivery systems such as ointments [5], creams [6], solutions [7], microparticles [8], tablets [9] and patches [10], tablets appear to be the most preferred formulation. The disadvantage of most of these mentioned delivery systems is that they get easily washed away by the continuous salivary secretion. Mucoadhesive tablets appear attractive because they can readily adhere to buccal cavity, are retained for longer period of time and can be removed at any time [11]. An ideal buccal dosage form should be able to 1) remain at the adhesive site for specified period, 2) provide unidirectional release of drug 2) exhibit sustained release profile when needed [12]. Considering and working on the above requirements, bilayer tablet of Diltiazem hydrochloride (DLZ) was addressed in current investigations, which may fulfil above expectations.

Diltiazem is a calcium channel blocker, which has been used in the treatment of various cardiovascular disorders, particularly angina pectoris and systemic hypertension [13]. It has a short biological half-life of about 3.5 hr and is rapidly eliminated [14]. The oral

bioavailability of diltiazem is 40 % in humans [15]. Because of its low bioavailability and short biological half-life attempts have been made to develop sustained release products with extended clinical effects and a reduced dosing frequency [16]. Drug which are highly water soluble are considered difficult to deliver in the form of sustained or controlled release formulation due to their susceptibility to dose dumping. As diltiazem hydrochloride is a highly water-soluble drug, its formulation into sustained or controlled release products is rather difficult. In the present investigation mucoadhesive tablets of diltiazem were formulated employing an interpolymer complex of acrylic acid and Poly (vinyl pyrrolidine) as mucoadhesive materials.

Carboxylic group containing polymers, such as polyacrylic acid possess good bioadhesive properties. Therefore, tremendous efforts have been focused on the polyacrylic acid based mucoadhesive drug delivery devices. A novel mucoadhesive polymer was prepared by following the procedure reported by Chun *et al* via template polymerization of acrylic acid in the presence of poly (vinyl pyrrolidine) [17]. The interpolymer complex (AAPVP) showed a greater force of adhesion than the commercially available mucoadhesive polymer Carbopol P 971 [17].

In current investigation an attempt has been made to design bilayer buccal tablets of diltiazem using a novel mucoadhesive polymer, AAPVP, to avoid its first pass metabolism and improve bioavailability. Additionally, the formulation was also designed for giving advantage of controlled release of diltiazem. The developed formulation was evaluated for ideal mucoadhesive formulation characteristics such as surface pH, % swelling, in vitro mucoadhesive force, *in vitro* release profile etc.

EXPERIMENTAL

Materials:

Acrylic acid purchased from Aldrich Chemical Co. (Milwaukee, WI) was used after vacuum distillation for removing the inhibitor. PVP K-25 was gifted by Signet chem. Ltd. and Azoisobisisobutyronitrile (AIBN) as an initiator was purchased from Aldrich Chemical Co. DLZ was gifted by Lupin Pharma. Ltd., India. All other chemicals were extra pure reagent grade and were used as received.

Preparation of polymer complexes:

AAPVP polymer complexes were synthesized as per the reported method [17]. Briefly, complexes were synthesized by template polymerization of acrylic acid in the presence of PVP as a template. To prepare the complexes, acrylic acid (1.7 mmol) and the appropriate amount of PVP were dissolved in 90 ml of ethanol and the solution was purged with nitrogen gas for 15-20 min to remove dissolved oxygen. The polymerization was carried with AIBN (0.5 mmol) as an initiator at 60 ^{0}C for 15 h. The supernatant was removed and the resulting precipitate was dissolved in dimethylformamide at 80 ^{0}C. The dissolved solution was poured into an excess of cold ethyl acetate with vigorous stirring. The resulting precipitate was dried in a vacuum oven at 60 ^{0}C for 24.

Preparation of Mucoadhesive Buccal Tablet

Direct double compression technique was employed for the formulation [18]. In this technique, first medicated layer was formed and backing layer blend was placed on first intermediate layer and compressed to get bilayer tablet. Compositions for the drug containing mucoadhesive layer are shown in Table 1. The physical blend of drug, polymers and excipients was properly mixed and passed through 20 mesh screen, then it was slightly compressed on single station tablet compression machine (Karunawati, Mumbai) using 8 mm flat faced punches to obtain intermediate tablet or loose compact. Similarly, blend of protective layer containing ethyl cellulose was compressed on the previously compressed medicated tablet or loose compact to get bilayer tablet.

Tablet Evaluation:

Technological parameters:

The diameter and thickness of the formulated tablets were measured using Vernier Caliper. Total weight of the tablets was noted.

Assay:

Twenty tablets from each batch were powdered individually and a quantity equivalent to 10 mg of DLZ was accurately weighed and extracted with a suitable volume of methanol. Each extract was suitably diluted and analyzed spectrophotometrically at 237 nm. Each measurement was carried out in triplicate and the results averaged. A blank solution containing all the components, except for the drug, was also prepared. Corresponding concentrations were calculated from the standard curve.

Surface pH Study:

The method adopted by Bottenberg *et al* was used to determine the surface pH of tablets [19]. A combined glass electrode was used for this purpose. Each tablet was allowed to swell by keeping it in contact with 1 mL of distilled water (pH 6.5 ± 0.05) for 2 hours at room temperature, and the pH was noted by bringing

the electrode into contact with the surface of the tablet and allowing it to equilibrate for 1 minute. The experiments were performed in triplicate, and average values were reported.

Swelling Study:
Buccal tablets were weighed individually (designated as W1) and placed separately in 2% agar gel plates, incubated at 37°C ± 1°C, and examined for any physical changes. At regular 1-hour time intervals until 6 hours, tablets were removed from the gel plates and excess surface water was removed carefully using the filter paper. The swollen tablets were then reweighed (W2) and the swelling index (SI) were calculated using the following formula [20]:

$$SI = [(W\,2 - W\,1)/\,W\,1] \times 100$$

The experiments were performed in triplicate, and average values were reported.

Ex vivo Mucoadhesive Strength:
Fresh sheep buccal mucosa was obtained from a local slaughterhouse and used within 2 hours of slaughter. The mucosal membrane was separated by removing the underlying fat and loose tissues. The membrane was washed with distilled water and then with phosphate buffer (pH 6.6) at 37°C.

The tablet's bioadhesive strength was measured on a modified physical balance using the method described by Gupta *et al* [21]. The fresh sheep buccal mucosa was cut into pieces and washed with phosphate buffer (pH 6.6). A piece of buccal mucosa was tied in the open mouth of a glass vial, filled with phosphate buffer (pH 6.6). This glass vial was tightly fitted into a glass beaker filled with phosphate buffer (pH 6.6, 37°C ± 1°C) so it just touched the mucosal surface. The tablet was stuck to the lower side of a rubber stopper with cyanoacrylate adhesive. Two pans of the balance were balanced with a 5 g weight on the right-hand side pan. The 5 g weight was then removed from the left-hand side pan, which lowered the pan along with the tablet over the mucosa. The balance was kept in this position for 5 minutes of contact time. The water was added slowly at 100 drops/min to the right-hand side pan until the tablet detached from the mucosal surface. The weight, in grams, required to detach the tablet from the mucosal surface provided the measure of mucoadhesive strength. The experiments were performed in triplicate, and average values were reported.

Ex vivo Residence Time:
The ex *vivo* mucoadhesion time was studied (n = 3) after application of tablets on freshly cut sheep buccal mucosa. The fresh sheep buccal mucosa was fixed in the inner side of a beaker, about 2.5 cm from the bottom, with cyanoacrylate glue. One side of each tablet was wetted with 1 drop of phosphate buffer (pH 6.6) and pasted to the sheep buccal mucosa by applying a light force with a fingertip for 30 seconds. The beaker was filled with 200 mL of phosphate buffer (pH 6.6) and was kept at 37°C ± 1°C. After 2 minutes, a 50-rpm stirring rate was applied to simulate the buccal cavity environment, and tablet adhesion was monitored for 6 hours. The time required for the tablet to detach from the sheep buccal mucosa was recorded as the mucoadhesion time [22].

In vitro Drug Release
The US Pharmacopoeia XXIII rotating paddle method was used to study drug release from the buccal tablets; 500 mL of phosphate buffer (pH 6.6) was used as the dissolution medium, at 37.0 ± 0.5°C, and a rotation speed of 50 rpm was used. One side of the buccal tablet was attached to the glass disk with instant adhesive (cyanoacrylate adhesive). The disk was put in the bottom of the dissolution vessel. Samples (1 mL) were withdrawn at one hour intervals and replaced with fresh medium. The samples were filtered through 0.45-µm Whatman filter paper and analyzed. The experiments were performed in triplicate, and average values were reported.

In vitro Buccal Permeation Study
The *in vitro* buccal permeation study of DLZ hydrochloride through the sheep buccal mucosa was performed using a *Keshary-Chien* type glass diffusion cell at 37°C ± 0.2°C. Sheep buccal mucosa was obtained from a local slaughterhouse and used within 2 hours of slaughter. Freshly obtained sheep buccal mucosa was mounted between the donor and receptor compartments. The tablet was placed on the mucosa, and the compartments were clamped together. The donor compartment was filled with 1 mL of phosphate buffer (pH 6.6). The receptor compartment (20 mL capacity) was filled with isotonic phosphate buffer (pH 7.4), and the hydrodynamics in the receptor compartment were maintained. At predetermined time intervals, a 1-mL sample was withdrawn and analyzed. The experiments were performed in triplicate, and average values were reported.

RESULTS AND DISCUSSION
The literature documents that the dose of DLZ can be reduced up to 80% *via* buccal delivery, owing to the avoidance of a hepatic first-pass effect [23]. Therefore, buccoadhesive matrices containing the lowest dose of DLZ, *i.e.*, 30 mg, were worked upon in the current study. Another work carried out on buccalformulation of DLZ corroborates the use of this dose level [24]. There

are reports indicating that the buccoadhesives have been studied for drug release up to 2 days [25]. However, as a buccoadhesive tablet, film or patch is unlikely to remain on the buccal mucosa for such long times, drug release in the present study was investigated only up to 6 hr. Preliminary studies carried out prior to the experimental design revealed that the tablets formed with very low AAPVP content exhibited 100% drug release, but were vulnerable to dose dumping. On the other hand, the tablets formed with very high polymer content showed undesirably slow release. Accordingly, a suitable range for each of the polymer amounts was selected as depicted in Table 1.

Formulation compositions are shown in Table 1. Total nine formulations were prepared employing different ratios of AAPVP and PVP K-30. Double direct compression technique was found satisfactory for formulation of bilayered DLZ tablets. Physicochemical parameters of the bilayered buccal tablets are depicted in Table 2. Diameter of the tablets ranged from 8.10 ± 0.10 to 8.22 ± 0.18 mm Thickness of the tablets were found to be from 3.20 ±0.40 to 3.270 ±0.16 mm. Total weight of formulated tablets were between 200.80 ± 2.42 to 203.45 ± 2.5mg. The above values were found satisfactory and within pharmacopoeial limits of variation. Assay values ranged from 97.8 ± 1.7 to 103.8 ± 1.6 %. The surface pH of all the formulations was within 5.9 ± 0.24 to 6.42 ± 0.8. It indicates that the surface pH of all formulations was slight acidic mimicking the oral pH environment and hence no mucosal irritation is expected. The lower pH was owed to acrylic acid content in the AAPVP matrix system. These results reveal that all the formulations provide an acceptable pH in the range of salivary pH (5.0-8.0) [26].

Swelling

The swelling of the bioadhesive formulation is an important prerequisite and crucial parameter for the phenomenon of bioadhesion[27]. Polymer swelling permits a mechanical entanglement by opening the bioadhesive sites for hydrogen bonding between the polymer and the mucosa. All the matrices were observed to be stable throughout the period of swelling (6 hr), with no fragmentation being apparent. All the developed formulations exhibited satisfactory swelling index required for mucoadhesion. The swelling index increased with increase in proportion of AAPVP and PVP K-30 in the formulation. Maximum swelling (48.2 %) was observed in F9, which contained maximum amount of AAPVP and PVP K-30. The difference in swelling of the polymers could be attributed to the difference in resistance of the matrix network structure to the water bonding [28]. Tablets containing constant amount of AAPVP exhibited higher degree of hydration with higher content of PVP K-30 (Table 2).

In vitro mucoadhesion

The importance of the ability of the polymer to take up water from the mucus has been shown to be a primary determinant of mucoadhesion [29, 30]. Adhesion occurs shortly after water uptake but adhesion will increase until the point where over hydration results in a drop in mucoadhesive strength due to disentanglement at the polymer/tissue interface [31]. The e*x vivo* mucoadhesive strength analysis indicated that the mucoadhesive strength was directly proportional to AAPVP content but inversely proportional to PVP K-30. Table 2 shows that the e*x vivo* mucoadhesive strength was increased linearly with increasing concentration of AAPVP after 5 minutes of contact time with sheep buccal mucosa. The increase in mucoadhesivity may be due to the formation of a strong gel that penetrates deeply into the mucin molecules. However, PVP K-30 had an inverse effect on e*x vivo* mucoadhesive strength, that is, as the concentration of PVP K-30 increased the e*x vivo* mucoadhesive strength decreased. Mucoadhesive forces of developed formulations were between 7.4 ± 0.4 N to 22.46 ± 2.2 N. The results show that gradual increase in force was obtained as proportion of AAPVP increased. Maximum force was shown by F7 (22.46 ± 2.2 N) which contained 56% AAPVP and 15 % PVP K-30. The e*x vivo* residence time of all the formulations (F1 to F9) with sheep buccal mucosa in phosphate buffer (pH 6.6) was more than 6 hrs.

Table 1: Composition of buccal tablet (DLZ-AAPVP)

Batch Code	F1	F2	F3	F4	F5	F6	F7	F8	F9
Medicated layer									
Drug (DLZ) (mg)	30	30	30	30	30	30	30	30	30
AAPVP (%)	28	28	28	42	42	42	56	56	56
PVP K-30 (%)	15	20	25	15	20	25	15	20	25
Talc (%)	1	1	1	1	1	1	1	1	1
Mag. Stearate (%)	1	1	1	1	1	1	1	1	1
Lactose (DC)	qs	qs	qs	qs	qs	qs	qs	qs	qs
Backing layer									
Ethyl cellulose (mg)	20	20	20	20	20	20	20	20	20
Total (mg)	200	200	200	200	200	200	200	200	200

Table 2: Physico-chemical properties of buccal tablet

Batch Code	Diameter (mm)	*Ex vivo* Mucoadhesion	Mucoadhesive Strength (N)	Thickness (mm)	Drug Content (%)	Surface pH	Swelling index
F1	8.14± 0.9	> 6 hrs	11.2± 2.2	3.20 ± 0.40	97.8± 1.7	5.9 ± 0.24	18.8
F2	8.10 ± 0.10	> 6 hrs	9.0± 0.2	3.24 ± 0.12	98.4± 1.24	6.0 ± 0.18	20.46
F3	8.20± 0.24	> 6 hrs	7.4± 0.4	3.20 ± 0.64	103.8± 1.6	6.0 ± 0.4	26.58
F4	8.16± 0.38	> 6 hrs	17.2± 1.4	3.21 ± 0.2	101.7± 0.4	5.9 ± 0.56	24.2
F5	8.10± 0.4	> 6 hrs	14.56± 1.2	3.25 ± 0.24	100.6 ± 0.8	6.14 ± 0.4	26.0
F8	8.18± 0.56	> 6 hrs	11.4± 1.6	3.26 ± 0.18	98.9 ± 1.2	6.5 ± .09	32.75
F7	8.16± 0.22	> 6 hrs	22.46± 2.2	3.27 ± 0.16	101.0 ± 1.0	5.8 ± 1.0	21.5
F8	8.20± 0.64	> 6 hrs	15.2± 1.2	3.22 ± 0.40	100.4 ± 0.85	6.12 ± 1.0	35.6
F9	8.22 ± 0.80	> 6 hrs	13.2± 2.6	3.26 ± 0.9	99.26 ±0.89	6.42 ± .8	48.20

In vitro release study

In vitro release of DLZ hydrochloride from different tablets is shown in Figure 1. Maximum drug release was observed in F3 containing 28% AAPVP and 42 % PVP K-30; it released 87.8 % of the drug in 6 h. The drug release rate appeared to increase with an increasing amount of the hydrophilic polymers but decrease with amount of AAPVA. The overall rate of drug release tended to decrease with increase in AAPVP content. This may be attributed to the fact that with an increase in hydrogel concentration, the viscosity of the gel layer around the tablet tends to limit further the release of active ingredient.

From the *in-vitro* drug release study from the DLZ tablets, it could be concluded that release rate could be modified by addition of the hydrophilic polymers. This observation was in good agreement with the results obtained by Wong *et al* [32]. The increase in rate of drug release could be explained by the ability of the hydrophilic polymers to absorb water, thereby promoting the dissolution, and hence the release, of the highly water-soluble drug. Moreover, the hydrophilic polymers would leach out and, hence, create more pores and channels for the drug to diffuse out of the tablets. This finding was also supported by the results of swelling studies where the highest swelling index was also exhibited by batches containing higher concentration of PVP K-30.

To investigate the kinetics of DLZ release from bilayered buccal tablets the release data was applied to, zero order, first order, Higuchi, Hixson-Crowell and Korsmeyer Peppas models and best fit was determined (Table 3). It is known that, if the values of release exponent (n) are in between 0 – 0.5 then it follows fickian diffusion and if n values lies in between 0.5 - 1.0 it supports non-fickian diffusion pattern. Summary of the drug release models used and their correlation coefficients are mentioned .Correlation coefficient can be utilized to find a suitable model. The results indicate that the release mechanism followed non-fickian diffusion pattern in all formulations indicating the combination of both diffusion and erosion controlled release mechanism (critical value of n = 0.539-0.767).

Table 3: Drug Release Parameters of Various Mucoadhesive Formulations Prepared as per Experimental Design

Formulation code	Zero order	First order	Higuchi	Hixson–Crowell	Release exponent (n)	Release model
F1	0.985	0.994	0.965	0.998	0.767	Hixson–Crowell
F2	0.970	0.996	0.981	0.996	0.691	Hixson–Crowell
F3	0.975	0.978	0.977	0.996	0.719	Hixson–Crowell
F4	0.936	0.973	0.988	0.962	0.613	Higuchi
F5	0.951	0.982	0.978	0.979	0.539	First order
F6	0.990	0.974	0.953	0.931	0.763	Zero order
F7	0.930	0.966	0.996	0.955	0.538	Higuchi
F8	0.970	0.994	0.979	0.989	0.666	Higuchi
F9	0.990	0.985	0.954	0.989	0.765	Zero order

Overall curve fitting showed that the drug release from controlled release mucoadhesive tablets followed differents release models. Formulation containing low amount of AAPVP (F1, F2 and F3) followed Hixon-crowell model which assumes that tablet may take spherical shape and dissolution can occur equally from all sides. Only batch F9, which was having highest amount of AAPVP and PVP K-30, followed zero order kinetics. Formulation F4 and F7 which was having low amount of PVP K-30 content followed Higuchi model which is most common for homogeneous polymer matrices. It describes drug release process based on Fick's law and release being dependent on square root of time. Formulations with lower level of polymers complex AAPVP exhibited higher burst release which can be ascribed to dissolution of the drug present initially at the surface of the matrix as the tablet imbibes water and starts swelling. As dissolution progresses, the gradual swelling of tablet creates proportionately new areas for drug diffusion. Since the matrix is hydrophilic, the permeation of dissolution medium takes place in the matrix and initiates dissolution of drug from the inner layers. All the tablets were optimized for investigation of i*n vitro* drug permeation through sheep buccal mucosa and a stability study in natural human saliva. The tablets had range of 27.6 % ± 1.10 to 36.1% ± 0.85 drug permeation in 6 hours (Figure 2).

Tablets were placed in humidity chamber at 40 $\pm$ 2^{o} and 75 $\pm$ 5 % RH for one month. Tablets were withdrawn every week and analysed for their drug content. Percentage drug present in the tablets was determined by UV spectrophotometrically. Percentage decreases in drug content was insignificantly in all the batches. It was found that the drug loss is less though the tablets were stored for one month. The tablets were also observed for their appearance and texture. These properties did not change in tablets during the period of study.

In nutshell, the addition of the interpolymer complex AAPVP significantly improved the bioadhesion of tablets but decreased the drug release, as shown in Figure 1. However, incorporation of the hydrophilic polymer PVP K-30 enhanced the drug release and swelling index but significantly decreased the mucoadhesive strength.

CONCLUSION

The results obtained in the present investigation indicate that the buccal tablet F 7 code containing 56 % AAPVP and 15% PVP-K 30 could be considered as optimized tablet prepared in terms of mucoadhesiveness and release profile and could be useful for buccal administration of Diltiazem hydrochloride. Further work is recommended to support its efficacy claims by long term Pharmacokinetic and Pharmacodynamic studies in human beings.

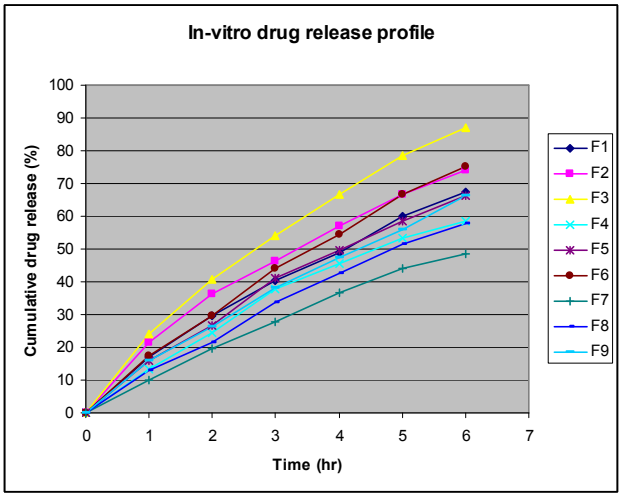

Figure 1 Cumulative drug release profile of 9 formulations

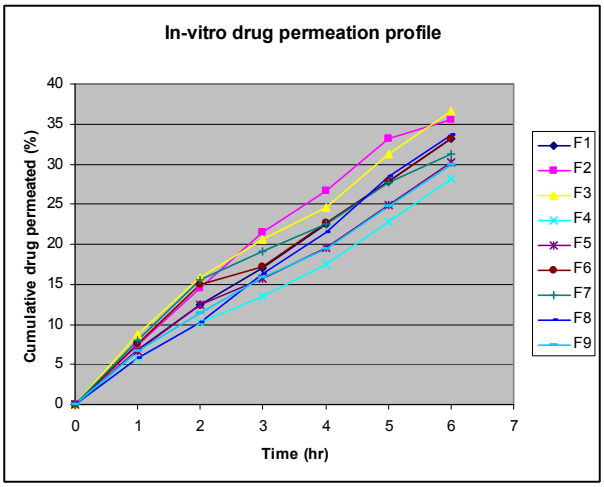

Figure 2 Cumulative drug permeation profiles of 9 formulations

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