

Review article**MECHANISM RESPONSIBLE FOR MUCOADHESION OF MUCOADHESIVE DRUG DELIVERY SYSTEM: A REVIEW**

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ABSTRACT: Mucoadhesion had been a topic of interest in the design of drug delivery system to prolong the residence time of the dosage form with the underlying absorption surface to improve and enhance the bioavailability of drugs. Mucoadhesion occurs between two surfaces, one of which is a mucous membrane and another is drug delivery system. Pharmaceutical aspects of mucoadhesion had been the subject of great interest during recent years because mucoadhesion could be a solution for bioavailability problems that result from a too short length of stay of the pharmaceutical dosage form at the absorption site within the gastro-intestinal tract. It had been a great challenge to the pharmaceutical sciences in order to enhance localised drug delivery or to deliver 'difficult' molecules (proteins and oligonucleotides) into the systemic circulation. Mucoadhesive systems remain in close contact with the absorption tissue, the mucous membrane releasing the drug at the action site leading to increase in bioavailability (both local and systemic effects). Extending the residence time of a dosage form at a particular site and controlling the release of drug from the dosage form are useful especially for achieving controlled plasma level of the drug as well as improving bioavailability. The main objective of this study was to selectively collect the data which were extended the gastrointestinal residence time of the dosage form and controlled the release of mucoadhesives.

Keywords: Bioadhesion, Mucoadhesion, Bioavailability, Gastrointestinal residence time, Mechanism of mucoadhesion.

INTRODUCTION

Bioadhesives are natural polymeric materials that act as adhesives. The term is sometimes used more loosely to describe a glue formed synthetically from biological monomers such as sugars, or to mean a synthetic material designed to adhere to biological tissue. (A.M. Smith and J.A.Callow, 2006). The term bioadhesion refers to any bond formed between two biological surfaces or a bond between a biological and a synthetic surfaces. (J.H. Bhatt, 2009). It may be defined as attachment of synthetic biological macromolecules to a biological tissue. A more specific term than bioadhesion is mucoadhesion. Mucoadhesion is the relatively new and emerging concept in drug delivery. Mucoadhesion is the special case of bioadhesion where the biological tissue is an epithelium covered by mucus. (Sumit Anand Abnawe, 2009). Most mucosal surfaces such as in the gut or nose are covered by a layer of mucus. Adhesion of a matter to this layer is hence called mucoadhesion. (A.M. Smith and J.A.Callow, 2006). Mucoadhesion keeps the delivery system adhering to the mucus membrane. (Ajay Semalty, 2006). Mucoadhesion can be defined as the ability of synthetic or biological macromolecules to adhere to mucosal tissues. (S.A. Sreenivas and K.V. Pai, 2008). The concept of mucoadhesion is one that has the potential to improve the highly variable residence times experienced by drugs and dosage forms at various sites in the gastrointestinal tract, and consequently, to reduce variability and improve efficacy. (J.O.Varum Felipe et.al., 2008). These systems remain in close contact with the absorption tissue, the mucous membrane, releasing the drug at the site of action leading to an increase in bioavailability. (Flavia Chiva Carvalho et.al., 2010).

Mucoadhesive drug delivery system prolong the residence time of the dosage form at the site of application or absorption and facilitate an intimate contact of the dosage form with the underline absorption surface and thus contribute to improved and / or better therapeutic performance of the drug (G.S.Asane, 2007) The mucoadhesive drug delivery system may include the following

1. Buccal delivery system.
2. Sublingual Delivery system.
3. Vaginal delivery system.
4. Rectal delivery system.
5. Nasal delivery system.
6. Ocular delivery system.
7. Gastro Intestinal delivery system. (Bibin K. Das and P. Deepa, 2009; G.S.Asane, 2007; S.B.Patil et.al.,2006, S.Ganga,2007; G.C. Rajput, 2010)

Their ability to stick to mucous membranes attracted attention as a pathway for resolving the problem of low bioavailability of traditional delivery systems used in the oral cavity and on the surface of the eye or other organs where movement of tissues or production of various secretions prevents prolonged retention of the medicinal agent.(Sumit Anand Abnawe, 2009). The reasons that the oral route achieved such popularity may be in part attributed to its ease of administration as well as the traditional belief that by oral administration the drug is well absorbed as the food stuffs that are ingested daily. (G.S.Asane, 2007). In the exploration of oral controlled release drug administration, one encounters three areas of potential challenge.

1. Development of a drug delivery system: To develop a viable oral controlled release drug delivery system capable of delivering a drug at a therapeutically effective rate to a desirable site for duration required for optimal treatment.
2. Modulation of gastro intestinal transit time: To modulate the GI transit time so that the drug delivery system developed can be transported to a target site or to the vicinity of an absorption site and reside there for prolonged period of time to maximize the delivery of a drug dose.
3. Minimization of hepatic first pass elimination: If the drug to be delivered is subjected to extensive hepatic first pass elimination, preventive measures should be devised to either bypass or minimize the extent of hepatic metabolic effect. (Y.W. Chien, 1992).

MUCOADHESIVE DRUG DELIVERY SYSTEM

DEFINITION

Adhesion can be defined as the bond produced by contact between a pressure - sensitive adhesive and a surface (D.E. Chickering and E.Mathiowitz, 1999; Jimenez-Castellanos, 1993). The American Society of testing and materials has defined it as the state in which two surfaces are held together by interfacial forces, which may consist of valence forces, interlocking action or both. (A.Ahuja, et.al., 1997) When the adhesion involves mucus or mucus membrane it is termed as mucoadhesion (J.H.Bhatt,2009)

CONCEPTS

In biological systems, four types of bioadhesion can be distinguished as follows:-

1. Adhesion of a normal cell on another normal cell.
2. Adhesion of a cell with a foreign substance.
3. Adhesion of a normal cell to a pathological cell.

4. Adhesion of an adhesive to a biological substance. (S.Ganga,2007; Jimenez-Castellanos, 1993; N.K.Jain,1997; G. Ponchel et.al., 1987)

MUCOUS MEMBRANE

Mucous membranes are the moist linings of the orifices and internal parts of the body that are in continuity with the external surface. They cover, protect, and provide secretory and absorptive functions in the channels and extended pockets of the outside world that are incorporated in the body. Mucus is a translucent and viscid secretion, which forms a thin, continuous gel blanket adherent to mucosal epithelial surface. The mean thickness of this layer varies from about 50-450 μm in humans. It is secreted by the goblet cells lining the epithelia or by special exocrine glands with mucus cells acini. The exact composition of the mucus layer varies substantially, depending on the species, the anatomical location and pathological states. (G.C. Rajput et.al.,2010). They secrete a viscous fluid known as mucus, which acts as a protective barrier and also lubricates the mucosal membrane. Mucosal membranes of human organism are relatively permeable and allow fast drug absorption. They are characterized by an epithelial layer whose surface is covered by mucus (Flavia Chiva Carvalho et.al.,2010) The primary constituent of mucus is a glycoprotein known as mucin as well as water and inorganic salts.(S.Ganga,2007). However, it has general composition.

Table 1: Composition of Mucous Membrane

S.NO.	COMPOSITION	%AMOUNT	REFERENCE
1	WATER	95	(G.C.Rajput et.al.,2010; S.E.Harding, 2003)
2	GLYCOPROTEINS &LIPIDS	0.5-5.0	
3	MINERAL SALTS	1	
4	FREE PROTEINS	0.5-1.0	

EXAMPLES OF MUCOSA

- Buccal mucosa.
- Oesophageal mucosa.
- Gastric mucosa.
- Intestinal mucosa.
- Nasal mucosa.
- Olfactory mucosa.
- Oral mucosa.
- Bronchial mucosa.
- Uterine mucosa.
- Endometrium (mucosa of the uterus).
- Penile mucosa.

FUNCTIONS OF MUCOUS LAYER

The mucous layer, which covers the epithelial surface, has various roles. (Bibin K. Das and P. Deepa, 2009; G.C.Rajput et.al.,2010; N.K.Jain,1997).

- 1.PROTECTIVE ROLE. 2.BARRIER ROLE. 3.ADHESION ROLE. 4.LUBRICATION ROLE.
- 5.MUCOADHESION ROLE.

1.PROTECTIVE ROLE: The Protective role results particularly from its hydrophobicity and protecting the mucosa from the lumen diffusion of hydrochloric acid from the lumen to the epithelial surface. (Bibin K. Das and P. Deepa, 2009; G.C.Rajput et.al.,2010)

2. BARRIER ROLE: The role of mucus layer as barrier in tissue absorption of drugs and other substances is well known as it influence the bioavailability of the drugs.The mucus constitutes diffusion barrier for molecules, and especially against drug absorption diffusion through mucus layer depends on molecule charge, hydration radius, ability to form hydrogen bonds and molecular weight.(Bibin K. Das and P. Deepa, 2009; N.K.Jain,1997).

3. ADHESION ROLE: Mucus has strong cohesive properties and firmly binds the epithelial cells surface as a continuous gel layer. (Bibin K. Das and P. Deepa, 2009; G.C.Rajput et.al.,2010; N.K.Jain,1997).

4. LUBRICATION ROLE: An important role of the mucus layer is to keep the membrane moist. Continuous secretion of mucus from the goblet cells is necessary to compensate for the removal of the mucus layer due to digestion, bacterial degradation and solubilisation of mucin molecules. (G.C.Rajput et.al.,2010; N.K.Jain,1997).

5. MUCOADHESION ROLE: One of the most important factors for bioadhesion is tissue surface roughness. (G.S.Asane,2007), Adhesive joints may fail at relatively low applied stresses if cracks, air bubbles, voids, inclusions or other surface defects are present. Viscosity and wetting power are the most important factors for satisfactory bioadhesion. (Bibin K. Das and P. Deepa, 2009; G.C.Rajput et.al.,2010) At physiological pH, the mucus network may carry a significant negative charge because of the presence of sialic acid and sulphate residues and this high charge density due to negative charge contributes significantly to the bioadhesion. (G.C.Rajput et.al.,2010)

NEED OF MUCOADHESIVE:

- Controlled release.
- Target & localised drug delivery.
- By pass first pass metabolism.
- Avoidance of drug degradation.
- Prolonged effect.
- High drug flux through the absorbing tissue.
- Reduction in fluctuation of steady state plasma level. (Sumit Anand Abnawe, 2009)

An ideal dosage form is one, which attains the desired therapeutic concentration of drug in plasma and maintains constant for entire duration of treatment. This is possible through administration of a conventional dosage form in a particular dose and at particular frequency. In most cases, the dosing intervals much shorter than the half life of the drug resulting in a number of limitations associated with such a conventional dosage form are as follows:

- Poor patient compliance; increased chances of missing the dose of a drug with short half-life for which frequent administration is necessary.
- A typical peak plasma concentration time profile is obtained which makes attainment of steady state condition difficult.
- The unavoidable fluctuation in the drug concentration may lead to under medication or over medication as the steady state concentration values fall or rise beyond in the therapeutic range.
- The fluctuating drug levels may lead to precipitation of adverse effects especially of a drug with small therapeutic index whenever overmedication occurs. (M. Bramhankar and S.B. Jaiswal,1995)

ADVANTAGES OF MUCOADHESIVES

- A prolonged residence time at the site of drug action or absorption.
- A localization of drug action of the delivery system at a given target site.
- An increase in the drug concentration gradient due to the intense contact of particles with the mucosal. (S.Ganga,2007; G.C.Rajput et.al.,2010).
- A direct contact with intestinal cells that is the first step before particle absorption. (K. Sachan Nikhil and A. Bhattacharya, 2009).
- Ease of administration.
- Termination of therapy is easy. {except gastrointestinal}
- Permits localization of drug to the oral cavity for a prolonged period of time.
- Can be administered to unconscious patients. except gastrointestinal}
- Offers an excellent route, for the systemic delivery of drugs with high first pass metabolism, thereby offering a greater bioavailability. (S. Punitha and Y. Girish, 2010).
- A significant reduction in dose can be achieved there by reducing dose related side effects.
- Drugs which are unstable in the acidic environment are destroyed by enzymatic or alkaline environment of intestine can be administered by this route. Eg. Buccal sublingual, vaginal. (K. Sachan Nikhil and A. Bhattacharya, 2009).
- Drugs which show poor bioavailability via the oral route can be administered conveniently.
- It offers a passive system of drug absorption and does not require any activation.
- The presence of saliva ensures relatively large amount of water for drug dissolution unlike in case of rectal and transdermal routes.
- Systemic absorption is rapid. (S.Ganga,2007; G.C.Rajput et.al.,2010).
- This route provides an alternative for the administration of various hormones, narcotic analgesic, steroids, enzymes, cardiovascular agents etc.
- The buccal mucosa is highly perfused with blood vessels and offers a greater permeability than the skin. (S. Punitha and Y. Girish, 2010).
- Less dosing frequency.
- Shorter treatment period.
- Increased safety margin of high potency drugs due to better control of plasma levels.
- Maximum utilization of drug enabling reduction in total amount of drug administered.
- Improved patient convenience and compliance due to less frequent drug administration.
- Reduction in fluctuation in steady state levels and therefore better control of disease condition and reduced intensity of local or systemic side effects. (S.Ganga,2007;15 G.C.Rajput et.al.,2010).

Despite the several advantages associated with oral controlled drug delivery systems, there are so many disadvantages, which are as follows:

- Basic assumption is drug should be absorbed throughout GI tract
- Limited gastric residence time which ranges from few minutes to 12 hours which lead to unpredictable bioavailability and time to achieve maximum plasma level. (G.C.Rajput et.al.,2010).

LIMITATIONS

- Drug administration via the buccal mucosa has certain limitations
- Drugs, which irritate the oral mucosa, have a bitter or unpleasant taste, odour, cannot be administered by this route.
- Drugs, which are unstable at buccal pH cannot be administered by this route.
- Only drugs with small dose requirements can be administered.
- Drugs may swallow with saliva and lose the advantages of buccal route.
- Only those drugs, which are absorbed by passive diffusion, can be administered by this route.
- Eating and drinking may become restricted.
- Swallowing of the formulation by the patient may be possible.
- Over hydration may lead to the formation of slippery surface and structural integrity of the formulation may get disrupted by the swelling and hydration of the bioadhesive polymers. (S. Punitha and Y. Girish, 2010).

STAGES OF MUCOADHESION

1. CONTACT STAGE 2. CONSOLIDATION STAGE.

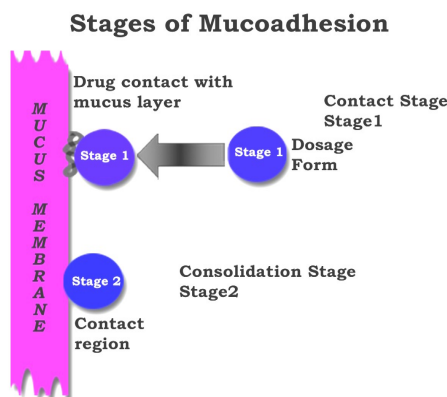


Fig. No.1. The two steps of the mucoadhesion process.

MECHANISM OF MUCOADHESION

The concept of mucoadhesion is one that has the potential to improve the highly variable residence times experienced by drugs and dosage forms at various sites in the gastrointestinal tract, and consequently, to reduce variability and improve efficacy. Intimate contact with the mucosa should enhance absorption. (J.O.Varum Felipe et.al., 2008) The mechanisms responsible in the formation of bioadhesive bonds are not fully known, however most research has described bioadhesive bond formation as a three step process:-

STEP1: Wetting and swelling of polymer

STEP2: Interpenetration between the polymer chains and the mucosal membrane.

STEP3: Formation of Chemical bonds between the entangled chains. (John D. Smart, 2005)

Step 1 :-The wetting and swelling step occurs when the polymer spreads over the surface of the biological substrate or mucosal membrane in order to develop an intimate contact with the substrate. (J.H.Bhatt,2009; Helene Hagerstrom, 2003) This can be readily achieved for example by placing a bioadhesive formulation such as a tablet or paste within the oral cavity or vagina. Bioadhesives are able to adhere to or bond with biological tissues by the help of the surface tension and forces that exist at the site of adsorption or contact. Swelling of polymers occur because the components within the polymers have an affinity for water. (Sheila Aidoo, 2009)

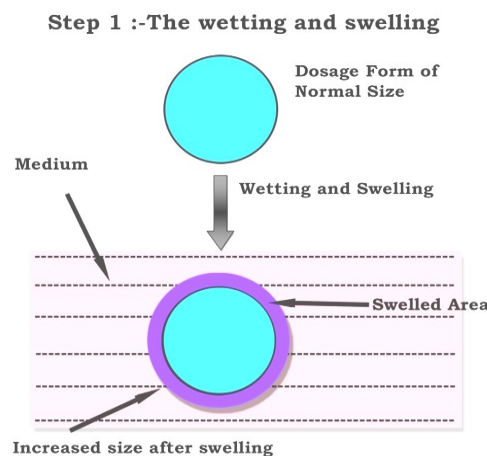


Figure. 2 Wetting and Swelling of Polymer

Step 2 : The surface of mucosal membranes are composed of high molecular weight polymers known as glycoproteins. In this step interdiffusion and interpenetration take place between the chains of mucoadhesive polymers and the mucous gel network creating a great area of contact.(Helene Hagerstrom, 2003; Hemanta Kumar Sharma et.al., 2009) The strength of these bond depends on the degree of penetration between the two polymer groups. In order to form strong adhesive bonds, one polymer group must be soluble in the other and both polymer types must be of similar chemical structure. (Sheila Aidoo, 2009 ; John D. Smart, 2005).

Step 3:- In this step entanglement and formation of weak chemical bonds as well as secondary bonds between the polymer chains mucin molecule. (Sheila Aidoo, 2009 ; Helene Hagerstrom, 2003) The types of bonding formed between the chains include primary bonds such as covalent bonds and weaker secondary interactions such as van der Waals Interactions and hydrogen bonds. Both primary and secondary bonds are exploited in the manufacture of bioadhesive formulations in which strong adhesions between polymers are formed. (Helene Hagerstrom, 2003).

Interdiffusion and Interpenetration

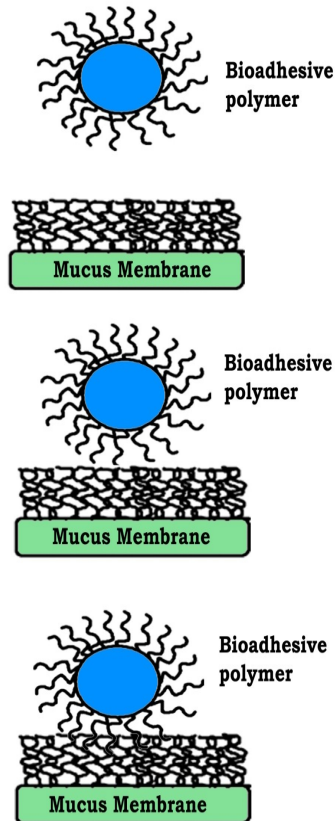


Figure. 3 Interdiffusion and Interpenetration of Polymer and Mucus

Formation of Chemical Bond

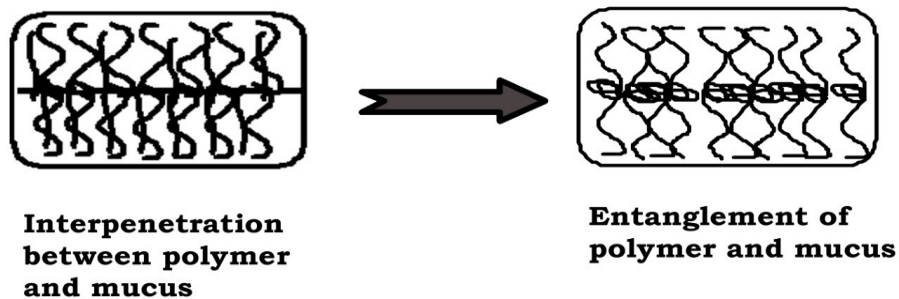


Figure. 4 Entanglement of Polymer and Mucus by Chemical bonds

Table 2 : Comparative Study of Different Mucoadhesive Formula

S.No	DRUG	CATEGORY	POLYMER	LIBERATION OF DRUG WITH MUCOADHESIVE	MUCOADHESIVE STRENGTH	MUCO ADHESIVE TIME	REFERENCE
1	ITRACONAZOLE	ANTIFUNGAL	CARBOPOL 934P HPMC	100% IN 3 HRS. IN 0.1N HCL	0.1916 ± 0.012 N 0.3392 ± 0.021 N		(Ashwini Madgulkar et al., 2008)
2	ROSIGLITAZONE MALEATE	ORAL HYPOGLYCEMIC	CARBOPOL 934.	75% IN 11 HRS. IN 0.1 N HCL	0.3922-0.4020 N	12-13 HRS.	(S.Shiva Krishna et al.,2006)
3	THEOPHYLLIN	CNS STIMULANT	HPMC CARBOPOL CHITOSAN	97% IN 10 HRS. IN HCL AT PH 1.2	0.4962± 0.015N 0.6413± 0.015N 0.7149± 0.009 N	10 HRS.	(V. Senthil et al.,2010)
4	GLIPIZIDE	ORAL HYPOGLYCEMIC	CHITOSAN	25% FOR 2-12 HRS. [IN VIVO]	–	12 HRS.	(JK Patel et al., 2005)
5	NYSTATIN	ANTIFUNGAL	CARBOPOL : HPMC [9:1]	80% IN 6 HRS. IN DISTILLED WATER	0.1961 N	6 HRS.	(J.M.Llabot et al., 2002)
6	CHLORPHENIRAMINE MALEATE	HALOGENATED ALKYLAMINE ANTIHISTAMINES.	POLYOXYETHYLE NE303 POLYOXYETHYLE NE301 POLYOXYETHYLE NE1105 POLYOXYETHYLE NE80	80% IN 5.5 HRS. IN DEIONIZED WATER	11 N 11N 8 N 4 N	MORE THAN 4 HRS.	(Deepak Tiwari et al., 2009)
7	THEOPHYLLIN ANHYDROUS	CNS STIMULANT	KARAYA GUM & GUAR GUM.	90% IN 12 HRS. IN HCL PH1.2	0.3002 ± 0.007 N	–	(V.N. Deshmukh et al., 2009)
8	MITOMYCIN-C	CHEMOTHERAPEUTIC AGENT	CHITOSAN	100% IN 24 HRS. IN PBS			(Muzaffer Erogluet al., 2002)
9	NONOXYNOL- 9	CONTRACETIVES	CARBOPOL 934	10% IN 7 HRS. IN CIRTRATE BUFER, PH 4.4 &PBS, PH 7.4	0.1892 ± 0.024 N		(Chi Hyun Lee and Y.W.Chien,1996)
10	BENZYLAMINE	NSAID	POLYACRYLIC ACID	75%IN 6 HRS. IN PBS, PH 6.8	–	–	(S.Burgalassi et al.,1996)
11	LIDOCAINE	LOCAL ANESTHETIC	POLYACRYLIC ACID	75%IN 5 HRS. IN PBS, PH 6.8	–	–	(S.Burgalassi et al.,1996)
12			CARBOPOL 971P POLYCARBOPHIL CMC CARRAGENAN	–	0.0438 ± 0.002 N 0.0361 ± 0.003 N 0.004± 0.002N 0.020± 0.002 N	IN 30 MINS.	(C.Eouani et al., 2001)
13	PREDNISOLONE	IMMUNOSUPPRESSANT	CHITOSAN	UPTO 88% IN 4 HRS. IN0.2M PBS,PH 6.8	–	–	(W.A. Sakchai et al., 2006)
14	CARVEDILOL	α-1 & β BLOCKER.	HPMC &CARBOPOL	86.26- 98.32 IN 90 MIN. IN PBS, PH 6.6	–	–	(J. Thimmasetty et al., 2008)
15	PROPRANOLOL HCL	β BLOCKER	SODIUM ALGINATE &CARBOPOL 934P	90 ± 2.87 IN 12 HRS. IN PBS, PH 6.8	0.2834 ± 0.009 N	20 ± 1.1 HRS.	(V.M. Patel et al., 2007)
16	FLURBIPROFEN	NSAID	HEC, HPMC, CARBOPOL	55%IN 12 HRS. IN SALIVA.	0.85 to 1.58 N	14 HRS.	(L. Perioli et al., 2007)
17	LISINOPRIL	ACE INHIBITOR	HEC, HPMC, CARBOPOL 934	97.1% IN 10 HRS. IN PBS, PH 6.8	0.3608 N		(Aditya Guda et al., 2010)
18	METOPROLOL TARTRATE	β1 BLOCKER	CARBOPOL 934: HEC (1:2)	74.41% IN 8 HRS. IN SALIVA	0.3383 N	–	(M.V. Ramana et al., 2007)
19	INSULIN	HYPOGLYCEMIC (HORMONE)	NaCMC-DVP	91.64% IN 6 HRS. IN PBS, PH 6.6	0.6227± 0.004 N		(J. Sahni et al., 2008)
20	GLIPIZIDE	ANTI-DIABITIC	CARBOPOL 934, HPMC, Na CMC	90% IN 6 HRS. IN PBS, PH 6.6	–	4.00 HRS.	(M. Semalty et al., 2008)
21	TERBUTALINE SULPHATE	β2 RECEPTOR AGONIST	HPMC	95.5% IN 12 HRS. IN PBS, PH 7.4	–	–	(R. Chanda et al., 2010)
22	BACLOFEN	ANTISPASTIC AGENT	CARBOPOL 974P, METHOCAL K15	98% IN 8 HRS. IN PBS, PH 6.8	0.1091± 0.006 N		(B. Gavaskar, et al., 2010)
23	CARVEDILOL	α-1 & β BLOCKER	HPMC-CARBOPOL	90.85% IN 1.5 HRS. IN PBS, PH 6.6	–	–	(J. Thimmasetty et al., 2008)
24	ACYCLOVIR	ANTIVIRAL	SODIUM ALGINATE	98.5% IN 8 HRS. IN 0.1N HCL	–	–	(S.B. Bhanjal et al., 2010)
25	NEOSTIGMINE BROMIDE	PARASYMPATHOMI METICS	CARBOPOL 974PNF, HPMC K15M	87.86% 84.5% IN 8 HRS. IN PBS, PH 6.4			(J. Rao et al., 2010)
26	MONTELUKAST	LEUKOTRINE RECEPTOR ANTAGONIST	PVP K 30 EUDRAGIT RL 100	67.35-93.62 IN 8 HRS. IN 0.5% SLS	–	–	(R. Rao et al., 2010)

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