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Erythromycin enteric recrystallized agglomerates for Directly Compressible Tablets

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ABSTRACT: The purpose of this research work was to obtain directly compressible enteric recrystallized agglomerates of erythromycin containing enteric polymers by emulsion solvent diffusion technique. Selected solvent for the process includes the best solvent (ethyl alcohol), non-solvent (distilled water) and bridging liquid (chloroform) according to their solubility in different organic solvent. The different enteric coating polymers like cellulose acetate phthalate (CAP), Eudragit S100 and Eudragit L100 were used in the crystallization system. The impact of these enteric coating polymers in drug: polymer ratio 1:0.25 and 1:0.5 on the release of erythromycin in 0.1N HCl were studied. The other physicochemical properties like flowability and packability were also studied. There is significant improvement in flowability and packability of enteric recrystallized agglomerates as compared to the raw crystals of erythromycin. The enteric recrystallized agglomerates having drug: polymer ratio 1:0.5 shows below 10% release of erythromycin in 0.1N HCl therefore selected for tablet preparation. The directly compressed tablets of these optimized enteric recrystallized agglomerates were prepared with microcrystalline cellulose (Avicel pH 102) and lactose monohydrate (Flowlac 200) as diluents. These prepared tablets shows below 10% release of erythromycin in 0.1N HCl and above 80% in phosphate buffer pH 6.8 which indicate that these tablets complies the release pattern as per the official pharmacopeia.
KEYWORDS: Direct compression, Erythromycin, Eudragit, cellulose acetate phthalate, Emulsion solvent diffusion.

INTRODUCTION:

Enteric coatings have been applied to solid oral dosage forms to improve the chemical stability of acid-sensitive drugs, to decrease gastric irritation and to target drug release to the colon (1-3). The enteric acrylic acid copolymers including Eudragit L100-55, Eudragit L100, Eudragit S100 and cellulose like cellulose acetate phthalate (CAP), are in widespread use today. Since dissolution is a function of the pH of the surrounding medium, mixtures of these polymers have been investigated for targeting drug delivery to the colon (4).

These polymers are sensitive to pH changes and are able to protect the drug from the degradation action of the enzymes and gastric fluid, which is very acid (pH = 1–2) (5-6), and also to avoid side effects such as gastritis for example in patients who consume aspirin daily. Thus, these materials should be very useful for the transportation of drugs which are distrusted in the gastric fluid to the intestine, protection of drugs of proteinic nature (7-8), and as cation-exchange membrane dependent of pH of media (9).

Film formation from organic polymer solutions results from the evaporation of the solvent, which initiates an increase in the polymer concentration and inter-diffusion of the polymeric chains. At higher polymer concentrations, an intermediate gel like stage is reached and, upon further evaporation of the solvent, a solvent-free polymeric film is obtained. Film formation from aqueous polymer dispersions is more complex. During coating, the colloidal polymer particles coalesce into a film that occurs concurrently with the evaporation of water (5).

Now days Kawashima and their co-workers developed a spherical crystallization technique that led to improving the flow and direct compressibility of number of pharmaceutical drug substances for enteric coating. Spherical crystallization was defined by Kawashima as "An agglomeration process that transforms crystals directly in to a compact spherical forms during the crystallization process." It also enables co-precipitation of drug & encapsulating polymer in the form of spherical particle. Improvement of dissolution profile was also achieved in some cases.

This technique involved selective formation of agglomerates of crystals held together by liquid bridges. Spherical crystallization technique has been successfully utilized for improvement of flowability & compressibility of crystalline drug, preparation of microsponges &

microspheres, masking of the bitter test. This technique could enable subsequent process such as separation, filtration, drying etc to be carried out more efficiently. Furthermore the resultant agglomerated crystals could be easily compounded with other pharmaceutical powders due to their spherical shape. It is the simple process that is also inexpensive enough for scaling up to a commercial level; this reduces time & cost by involving faster operation, less machinery & fewer personnel with great advances in tabletting technology, especially the introduction of number of directly compressible excipients. By using this technology, physicochemical properties of pharmaceutical crystals dramatically improved for pharmaceutical process i.e. milling, mixing & tabletting because of their excellent flowability & packability.

Erythromycin is a typical representative of the macrolide group of antibiotics and is produced by Streptomyces erythreas. Clinically it is widely used in the treatment and prevention of diseases. Like penicillin G it is a broad spectrum antibiotic and it is effective against most gram negative and positive bacteria compared to other antibiotics.

The side-effects are relatively low (6). Current indications for the drug include: respiratory infections, whooping cough, Legionnaires disease and Campylobacter enteritis. Erythromycin is also known to be active against penicillin resistant staphlococcus; chlamydia and mycoplasma.Erythromycin base is a white, bitter, crystalline substance that is poorly soluble in water. It is a weak basetion by stomach acid and this culminates in decreased absorption following exposure to gastric secretions. (7) Modifications of the drug and its product formulations have attempted to improve absorption and subsequent serum levels by two methods. One involves providing a protective enteric coating to shield erythromycin base from acid degradation in the upper-gastro-intestinal tract. The other involves altering the chemical structure of erythromycin molecule itself to decrease acid inactivation.

In the present work, an innovative method was employed to prepare enteric recrystallized agglomerates of Erythromycin. Enteric-coated products are designed to remain intact in the stomach and then to release the active substance in the upper intestine. The enteric recrystallized agglomerates were prepared by emulsion solvent diffusion technique. Two polymers offered resistance for gastric erosion; enteric cellulose based polymer cellulose acetate phthalate (CAP) and the enteric acrylic acid copolymers including Eudragit L100 and Eudragit S100.Evalvate the prepared enteric recrystallized agglomerates of erythromycin for in vitro release of erythromycin from recrystallized agglomerates in 0.1N HCl and phosphate buffer pH 6.8 and other physicochemical properties. Prepared the tablet dosage form of enteric recrystallized agglomerates with directly compressible excipients.

MATERIALS AND METHOD:

Materials:

Erythromycin base was obtained from Alembic Research center (Vadodara, Gujarat, India).Cellulose acetate Phthalate (CAP), Eudragit E100 were obtained as gift samples from Sun pharmaceuticals (Vadodara, Gujarat, India).Ethanol, dichloromethane, polyvinyl alcohol(PVA) and other solvents was obtained from Loba Chemicals (Mumbai, India).

Method:

Emulsion solvent diffusion method:

The recrystallized spherical enteric coated agglomerates were obtained by the emulsion solvent diffusion method using distilled water as an external phase. The internal phase consisted of a good solvent (ethanol) and a bridging liquid (chloroform) with erythromycin and enteric coating polymers.

At first, the Erythromycin (2gm) and polymer as per mentioned in below table were co-dissolved in an organic solvent mixture that was composed of 10mL ethanol (good solvent) and 5mL chloroform (bridging liquid). The drug polymer solution was slowly injected via a syringe into the 0.5% PVA in distilled water as external phase (poor solvent) under agitating. The system was stirred continuously for about 30 minutes during which the good solvent diffusing into the poor solvent; the droplets gradually solidified and formed spherical recrystallized agglomerated crystals of erythromycin with enteric coated polymers. Then, the system was filtered to separate the recrystallized enteric agglomerates from the preparation system. The resultant product was washed with distilled water and dried in an oven at 40^0C for 12 hrs. The whole process was carried out at room temperature.

Different polymers in formulation:

Three different types of Acrylic polymers (Eudragit-L100, Eudragit-S100) were employed to determine the effect of Eudragit type on their enteric coated property

Different Erythromycin: Polymer Ratios :(1:0.05, 1:0.10, 1:0.15, and 1:0.2) were used in order to investigate the effect of Drug: Polymer ratio on the drug release in 0.1N HCl and phosphate buffer pH 6.8.

Standard calibration curve:

Two hundred of previously dried to constant weight erythromycin was weighed into 100mls volumetric flask. Anhydrous ethanol was used to dissolve and dilute to a solution

containing 2mg/ml of erythromycin 10.0mls of the solution was measured accurately into a 50ml volumetric flask and glacial acetic acid was added to volume. The following volumes (0.5, 1.0, 1.5 2.0, 2.5 3.0 mls) were pipetted into a 10 ml volumetric flask. One ml of bromocresol purple and 3.0 mls of hydrochloric acid was added. Glacial acetic acid was used to top each to volume. It was shaken and allowed to stand still for 10 minutes. The absorbance was determined at 480nm.

Drug content determination:

The recrystallized enteric agglomerates equivalent to 50mg of erythromycin was added into a 100ml

volumetric flask. It was dissolved using anhydrous ethanol and diluted to volume. The solution was shaken vigorously and filtered. Ten mls of the filtrate were measured accurately into a 50 millilitre volumetric flask, and glacial acetic acid added to volume. One ml was pipetted into a 10mls volumetric flask 1.0mls of bromocresol purple indicator, and 3.0mls of hydrochloric acid was also added. It was shaken and allowed to standstill for 10 minutes. At wavelength 480nm the absorbance was determined.

Flow properties determination:

Flow properties of the drug and prepared melt granules were studied by determining the bulk density (σb), tap density (σt), Carr's Index and Hausner ratio. A weighed quantity of the samples was taken to determine the bulk and tap density. The properties were determined using following equations.

Bulk density (σb) = Mass / Poured volume (1)

Tap density (σt) = Mass / Tapped volume (2)

Carr's Index = [(σt – σb) / σt] x 100 (3)

Hausner ratio = (σt / (σb) (4)

Measurement of Packability:

The packability of the samples was investigated by tapping them in to a 25-ml measuring cylinder using a tapping machine. Initially, 25 g of substance was weighed and then was gently poured into a measuring cylinder. The volume of 25 g samples was recorded. The poured density (minimum density) was calculated from the powder mass (25 g) and the volume. Then the cylinder was tapped and the volume was recorded after every 100 taps until the volume did not change significantly. The compressibility was evaluated by measuring the tapped density according to the modified Kawakita (I) and Kuno (II) equation

$N/C = 1/(ab) + N/a$.....I

Where as {$C = (Vo-Vn)/Vo$, $a = (Vo-V\infty)/Vo$.}

N =Number of tapping, C =Difference in volume (degree of volume reduction.), a and b = constant for packability and flowability, Vo = Initial volume, Vn = Final volume after nth tapping, V∞ = Powder bed volume at equilibrium.

$\rho f - \rho n = (\rho f - \rho o) . \exp. (-kn)$…II

Where as ρf, ρo, ρn Apparent densities at equilibrium, nth tapped, initial state respectively

The compressibility was assessed by comparing the constants a, 1/b and k in Eqs. I and II, respectively. The constant a represents the proportion of consolidation at the closest packing attained and constant 1/b describes cohesive properties of powders or the apparent packing velocity obtained by tapping. The constant k in Kuno's equation represents the rate of packing process.(8-9)

Dissolution of Enteric recrystallized agglomerates in 0.1N HCl:

The prepared recrystallized enteric agglomerates were tested for its stability in 0.1N HCl. Recrystallized agglomerates containing 100mg of erythromycin was examined in 0.1N HCl at the speed of 100rpm having temperature $37^0C \pm 0.5^0C$ for two hour. The samples were added into a separating funnel. To it add bromocresol purple and chloroform to extract twice. The absorbance was taken at 480nm wavelength to determine the release of erythromycin in 0.1N HCl.

Preparation of Erythromycin enteric tablets:

Tablets ingredients were accurately weighed (Mettler Toledo B204-S) as mentioned in table 1. These powders were then passed through 20 mesh sieve. Erythromycin enteric recrystallized agglomerates, microcrystalline cellulose (Avicel Ph 102) and Lactose monohydrate were mixed in a large poly bag using tumbling action. Finally magnesium stearate was added and again mixed for 5 minutes so that particle surface was coated by lubricant evenly. The blend was compressed using single punch tablet machine, having concave punches.

In vitro release study of enteric tablet:

Six tablets were examined in 0.1N HCl at the speed of 100rpm having temperature $37^0C \pm 0.5^0C$ for two hour. The samples were added into a separating funnel. To it add bromocresol purple and chloroform to extract twice. The absorbance was taken at 480nm wavelength to determine the release of erythromycin in 0.1N HCl. If the release is below 10% than continue the dissolution study in Phosphate buffer pH 6.8.

The same six tablets were examined in simulated intestinal juice (pH 6.8) phosphate buffer medium. Samples were taken after 5, 15, 30 and 60 minutes, and each time 5.0 mL of sample was taken and replace same quantity of fresh phosphate buffer to maintain sink condition.

RESULTS AND DISCUSSION:

From the solubility study of Erythromycin base in different solvents, drug shows the solubility (mg/ml) like chloroform (100), ethanol (450), and water (0.92). From the solubility data of Erythromycin base the good solvent (ethanol), bridging agent (chloroform) and poor solvent (distilled water) were selected for the spherical crystallization process. Chloroform was chosen as bridging liquid because of its excellent drug wettability and immiscibility with the dispersion medium. Quantity of the selected solvent was determined by using Scheffe third degree incomplete model. The selection of optimized temperature difference between drug solution and dispersion medium (25^0C) and agitation speed 1000 ± 50 with optimized drug: polymer ratio 1:0.5.

The method used for the preparation of agglomerated crystals was Quasi-Emulsion Solvent Diffusion method (QESD), in which droplets of solvent formed the quasi emulsion. The continuous phase is a liquid in which the drug solution is immiscible, crystallization occurs inside the droplets because of counter diffusion of solvents through the droplets. The average diameter of the agglomerated crystals increased with increasing content of chloroform in the system due to the enhanced agglomeration of powdery crystals. When the amount of ethanol in the system was increased while the amount of chloroform keeping constant, the diffusion rate of ethanol and chloroform from the droplets were enhanced with increasing the content of ethanol in the system. The

increase in diffusion rate of chloroform from droplets shortens the agglomeration process of the crystals produced in the droplets. Decrease in chloroform content of droplets reduces the agglomeration force of the crystal due to increase in the unwatted part of the crystals with chloroform in the agglomerates resulting in formation of flocks produced with pendular bridges of water. Thus diameter and recovery of agglomerates decreased with increasing the ethanol content in the system. The all agglomerated crystals showed drug content between 97-99%.

Table: 2 Represents flowability parameters of the erythromycin and recrystallized enteric agglomerated crystals in term of Carr index and Hausnar ratio. Recrystallized enteric agglomerated crystals were found to have significantly lower cars index and hausner ratio (** $P<0.01$) in comparison to the raw crystals of erythromycin , which could be due to the irregular stone shaped crystals of erythromycin which hindered in the uniform flow of crystals from funnel. The reason for the excellent flowability of recrystallized enteric agglomerated crystals was due to significant reduction in interparticle fraction because of their agglomerated spherical shape with reduction in the surface area.

Packing process of the agglomerated crystals in a measuring cylinder by tapping was described by Kawakitas and Kunos equation. Agglomerates were easily packed by tapping, the process of which was evaluated based on percent compressibility (Carr, 1965) and parameters of the Kawakita equation (Kawakita and Tsutsumi, 1966).

The packing ability was assessed by comparing the constants **a, b** and **k** in above equation. The reciprocals of **b** and **k** represent the packing velocity. The constant **a** for the agglomerated crystals was smaller then the raw unagglomertaed crystals of macrolide antibiotics. This indicated that the agglomerated crystals were easily packed, even without tapping. The larger **b** values of the agglomerated crystals proved that the packing velocity of the agglomerated crystals by tapping was slower then that of the crystals which are not agglomerated. The smaller **k** in kuno equation for the agglomerated crystals coincidence with the above findings. The slow packing velocity corresponded with the proportion of the consolidation of powder bed per tap, which is slow.

The lower value of **a** in Kawakitas equation for agglomerated crystals then that of original macrolide antibiotics crystals, while **b** in kawakitas equation and **k** in kunos equation where both higher. These indicated that the agglomerated crystals had excellent flowability and packability in terms of handling properties in tablet preparation such as feeding into die and their direct toileting behavior. These findings proved that the flowability and packability of agglomerated crystals were preferably improved for direct tabletting.These findings also suggest that agglomerates flow and pack smoothly from the hopper into the dies and that the tablets formed from agglomerates attain uniformity in weight.

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The in vitro release studies of erythromycin from the enteric recrystallized agglomerates were carried out in 0.1N HCl to ensure the resistance of enteric recrystallized agglomerates to release the erythromycin in 0.1N HCl. The enteric recrystallized agglomerates having drug: polymer 1:0.25 shows drug release above 10% in 0.1N HCl while drug: polymer 1:0.5 shows drug release below 10% therefore for the preparation of tablet enteric recrystallized agglomerates having drug: polymer 1:0.5 were selected.

Tablet manufacturing by direct compression has increased progressively over the years. It offers advantages over the other manufacturing processes for tablets, such as wet granulation and provides high efficiency. As direct compression is more economic, reducing the cycle time and straight forward in terms of good manufacturing practice requirements. On the other hand wet granulation not only increases the cycle time, but also has certain limits imposed by thermolability and moisture sensitivity of the active. So pharmaceutical industry is now focusing increasingly on direct tableting process.

When formulating direct compression tablets, the choice of binder or diluents is extremely critical since a slight variation in the binder ratio can lead to capping, lamination, chipping and friable tablets and all of these are common defects experienced with direct compressible formulations. Here, microcrystalline cellulose (Avicel PH 102) and lactose monohydrate (Flowlac 200) was used as filler which showed excellent compressibility with the prepared recrystallized enteric agglomerates. It is self-lubricating (10) and adds compact and strength into the tablets considerably (11). Magnesium stearate was selected as lubricant, which gives; a uniform flow from hopper to die. It prevents the adhesion of tablet material to the machine parts such as punches and dies, reduce inter particle friction and facilitates the ejection of tablets from the die cavity. It is hydrophobic and may retard the dissolution of a drug from a solid dosage form; the lowest possible concentration is therefore used in such formulations.

The prepared tablets were evaluated for in vitro release in 0.1N HCl as well as phosphate buffer pH 6.8.The all prepared tablet formulation shows below 10% release in 0.1N HCl within 2 hrs and above 80% release in phosphate buffer pH 6.8 within 60 minutes. Therefore these tablets complies the release pattern as per official pharmacopoeia.

CONCLUSIONS:

Erythromycin, a lipophlic macrolide antibiotic which is destructed in gastric acid was successfully converted into enteric recrystallized agglomerates by novel emulsion solvent diffusion method. The prepared enteric recrystallized agglomerates show significant improvement in flowability and packability as compared to the raw crystals of erythromycin. The prepared tablets form these enteric recrystallized agglomerates show the release pattern as per the pharmacopoeial specifications.

Table: 1 Formulation of Erythromycin enteric coated recrystallized agglomerates.

Sr.No	Polymer used	Drug: polymer ration	Product Code
01	Eudragit L100	1:0.25	ETML1
02	Eudragit L100	1:0.5	ETML2
03	Eudragit S100	1:0.25	ETMS1
04	Eudragit S100	1:0.5	ETMS2
05	Cellulose acetate phthalate(CAP)	1:0.25	ETMCAP1
06	Cellulose acetate phthalate(CAP)	1:0.5	ETMCAP2

Table: 2 Evaluation of recrystallized enteric erythromycin base agglomerates.

Product Code	Evaluation parameters				% release in 0.1N HCl	Packability study		
	Product yield	Content	Carr index	Hausnar ratio		a	b	k
ETM	NA	97 ±1.36	29 ±0.56	1.97 ±0.35	NA	0.353	0.0028	0.0125
ETML1	85 ±2.56	95 ±1.86	18 ±0.75	1.22 ±0.23	15 ± 0.856	0.139	0.0081	0.0051
ETML2	90 ±1.65	93 ±2.10	15 ±0.65	1.05 ±0.36	8 ± 0.693	0.214	0.0049	0.0045
ETMS1	86 ±1.96	95 ±2.56	11 ±0.55	1.11 ±0.15	10 ± 0.456	0.182	0.0070	0.0062
ETMS2	92 ±2.34	95 ±1.89	13 ±0.45	1.17 ±0.24	5 ± 0.159	0.197	0.0080	0.0040
ETMCAP1	85 ±2.56	93 ±1.75	12 ± 0.65	1.20 ±0.26	12 ± 0.357	0.210	0.0095	0.0035
ETMCAP2	90 ±1.69	94 ±1.56	14 ±0.35	1.13 ±0.34	6 ± 0.428	0.186	0.0085	0.0055

Table: 3 Formulation of directly compressible erythromycin enteric tablet

Sr. No.	Name of Ingredients (mg/tab.)	Tablet Code		
		ETM1	**ETM2**	**ETM3**
1	ETML2 Agglomerates (Equiv. 250mg ETM)	**375**	**-----**	**-----**
2	ETMS2 Agglomerates (Equiv. 250mg ETM)	**-----**	**375**	**-----**
3	ETMCAP2 Agglomerates (Equiv. 250mg ETM)	**-----**	**-----**	**375**
4	Microcrystalline cellulose	**35**	**35**	**35**
5	Lactose monohydrate	**25**	**25**	**25**
6	Magnesium stearate	**5**	**5**	**5**
Quantity per tablet (mg)		**440**	**440**	**440**

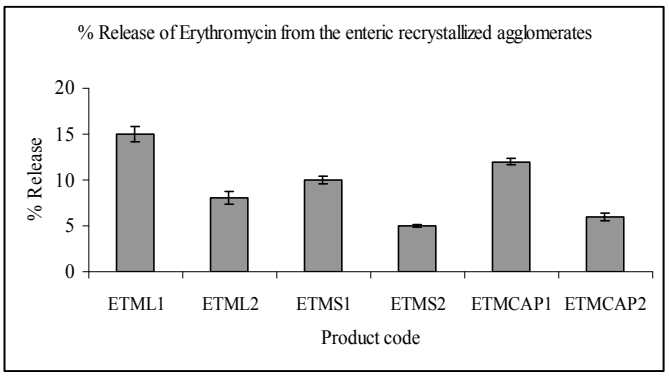

Figure: 1 In vitro release of erythromycin from enteric recrystallized agglomerates.

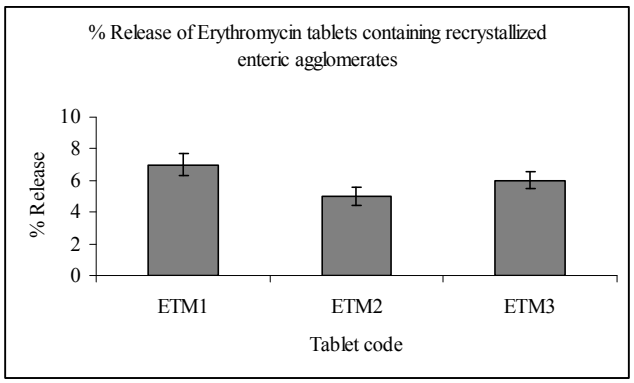

Figure: 2 In vitro release of erythromycin from tablets containing enteric recrystallized agglomerates.

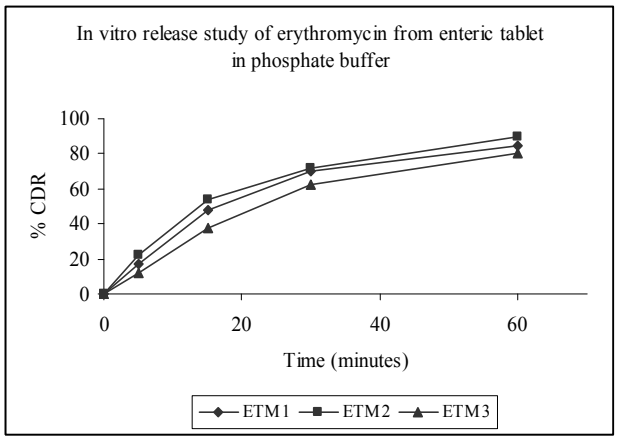

Figure: 3 In vitro release of erythromycin from tablets containing enteric recrystallized agglomerates in phosphate buffer pH 6.8.

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REFERENCES:

1. Khan M.Z.I., Prebeg Z., Kurjakovic N.,A pH-dependent colon targeted oral drug delivery system using methacrylic acid copolymers. I. Manipulation of drug release using Eudragit® L100-55 and Eudragit® S100 combinations. J. Control. Release. 1999, 58, 215–222.
2. Ashford M., Fell J.T., Attwood D, Woodhead P.J., An in vitro investigation into the suitability of pH-dependent polymers for colonic targeting. Int. J. Pharm. 1993, 91, 241–245.
3. Rijk M.C.M., van Schaik A., van Tongeren J.H.M., Disposition of 5-aminosalicylic acid by 5-aminosalicylic acid delivering compounds. Scand. J. Gastroenterol. 1988, 23, 107–112.
4. Khan M.Z.I., Stedul H.P., Kurjakovic N., A pH-dependent colon targeted oral drug delivery system using methacrylic acid copolymers. II.Manipulation of drug release using Eudragit® L100 and Eudragit® S100 combinations. Drug Dev. Ind. Pharm. 2000, 26, 549–554.
5. Wheatley T.A., Steuernagel C.R., Latex emulsion for controlled drug delivery. In: McGinity, J.W. (Ed.), Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms. Dekker, New York, pp., 1997, 1–54.
6. Carter BL, Woodhead JC, Cole JK and Mlavetz G.Gastrointestinal side effects with erythromycin preparations. Drug Intelligence and Clinical Pharmacy. 1987, 21, 734-736.
7. Meade RH. III Drug therapy reviews, antimicrobial spectrum pharmacology and therapeutic use of erythromycin and its derivatives American Journal of Hospital Pharmacy. 1979,36,1185 – 89.
8. Kawashima Y., Imai M., Takeuchi H., Yamamoto H and Kamiya K., Development of agglomerated crystals of Ascorbic acid by the spherical crystallization techniques, KONA. 2002, 20 (3), 251-61.
9. Morshima K, Kawashima Y, Takeuchi H, Niwa T and Hino T. Tabletting properties of Bucillamine agglomerates prepared by the spherical crystallization technique. Int Jr Pharm 1994; 105: 11-18.
10. Omray A and Omray P., Evaluation of microcrystalline cellulose as a glidant. Indian J.Pharm. Sci., 198648: 20-22.
11. Hernier AP and Teleman O., Interface between Monoclinic Crystalline Cellulose and Water: Break down of the oddf even duplicity. Langmuir.1997, 13,511-518.

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